US 20170189546A1

(19) **United States**

(12) **Patent Application Publication**

Bidwell, III et al.

(10) **Pub. No.: US 2017/0189546 A1**

(43) **Pub. Date: Jul. 6, 2017**

(54) **OCULAR COMPOSITIONS AND METHODS THEREOF**

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(21) Appl. No.: **15/307,335**

(22) PCT Filed: **Apr. 29, 2015**

(86) PCT No.: **PCT/US15/28348**

§ 371 (c)(1),
(2) Date: **Oct. 27, 2016**

Related U.S. Application Data

(60) Provisional application No. 61/985,808, filed on Apr. 29, 2014.

Publication Classification

(51) **Int. Cl.**

A61K 47/48	(2006.01)
A61K 9/06	(2006.01)
A61K 38/17	(2006.01)
A61K 9/00	(2006.01)
A61K 38/45	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 47/48246*** (2013.01); ***A61K 9/0048*** (2013.01); ***A61K 9/06*** (2013.01); ***A61K 38/45*** (2013.01); ***C12Y 207/10001*** (2013.01); ***A61K 38/1703*** (2013.01)

(57) **ABSTRACT**

Methods and pharmaceutical compositions (or delivering a therapeutic agent, treating a neovascularization disorder, and treating an ocular infection include make use of a compound that includes an clastin-likc polypeptide (ELP) coupled to a therapeutic agent, wherein the ELP comprises at least one repeat of the amino acid sequence VPGXG (SEQ ID NO: 1), and where the composition is suitable for ocular administration.

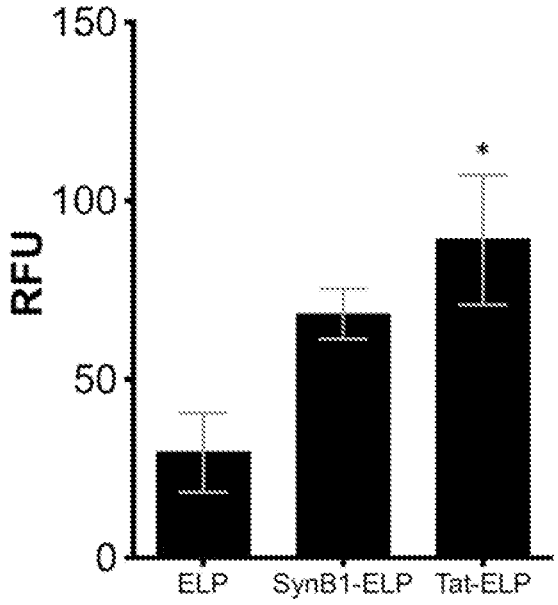


Figure 1

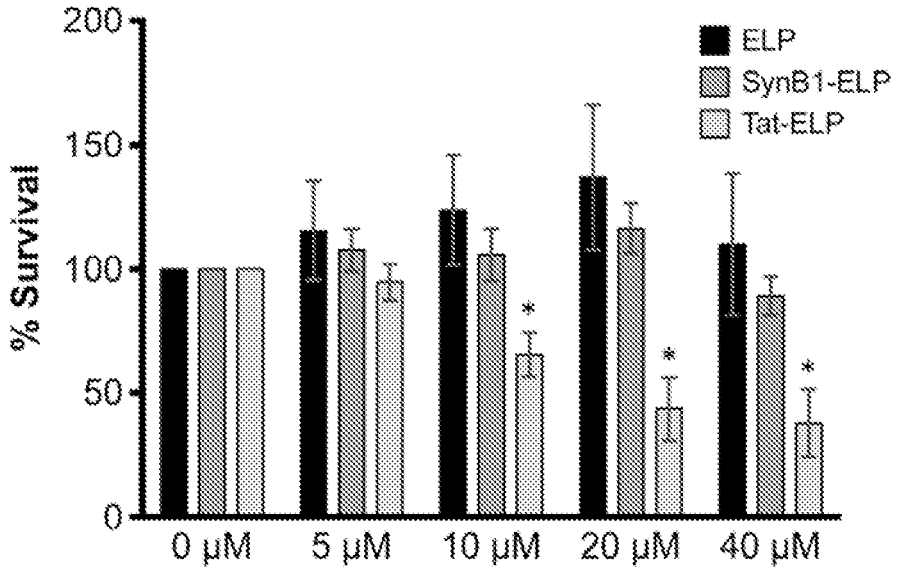
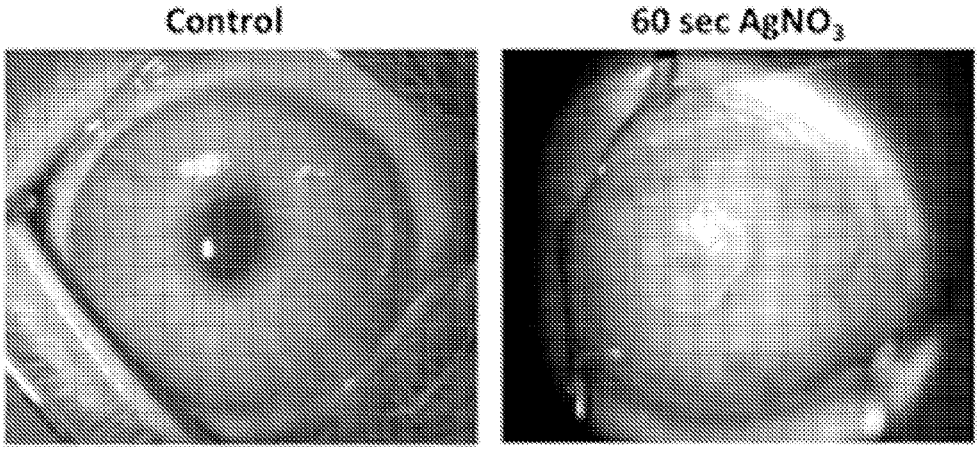


Figure 2



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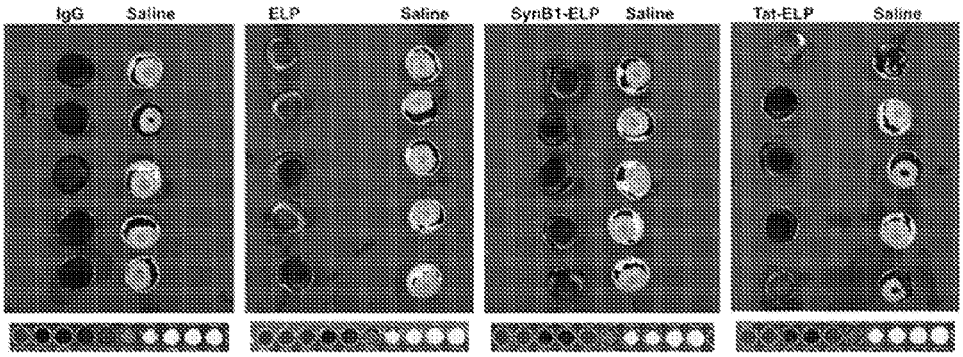

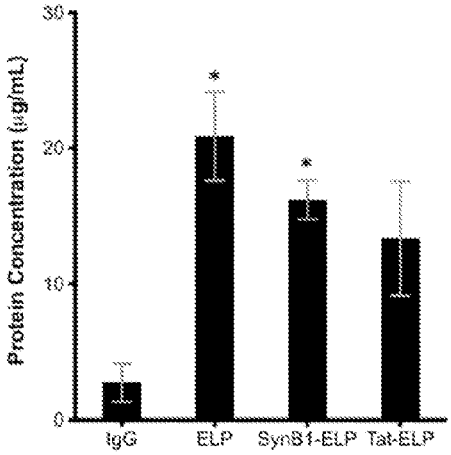

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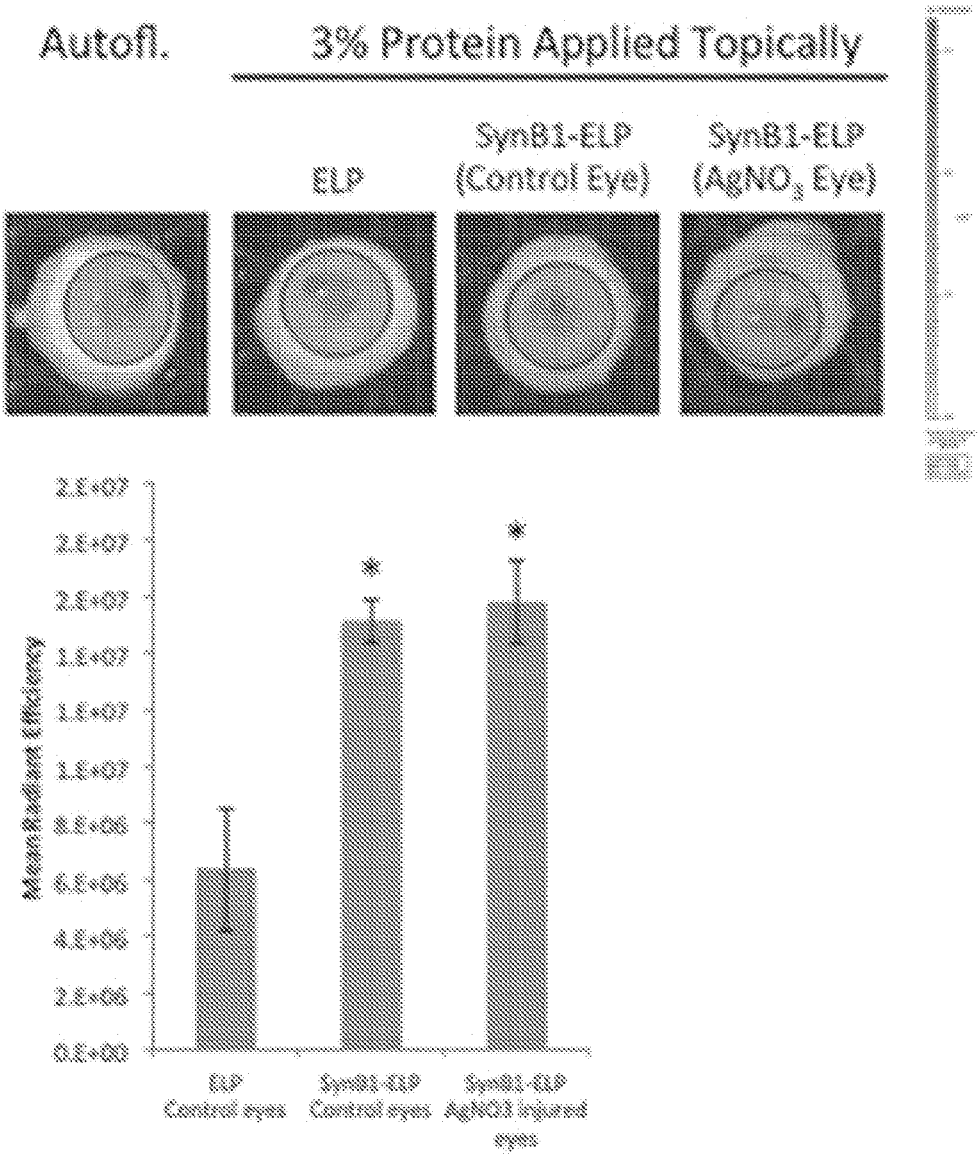

Figure 4 (Con't)

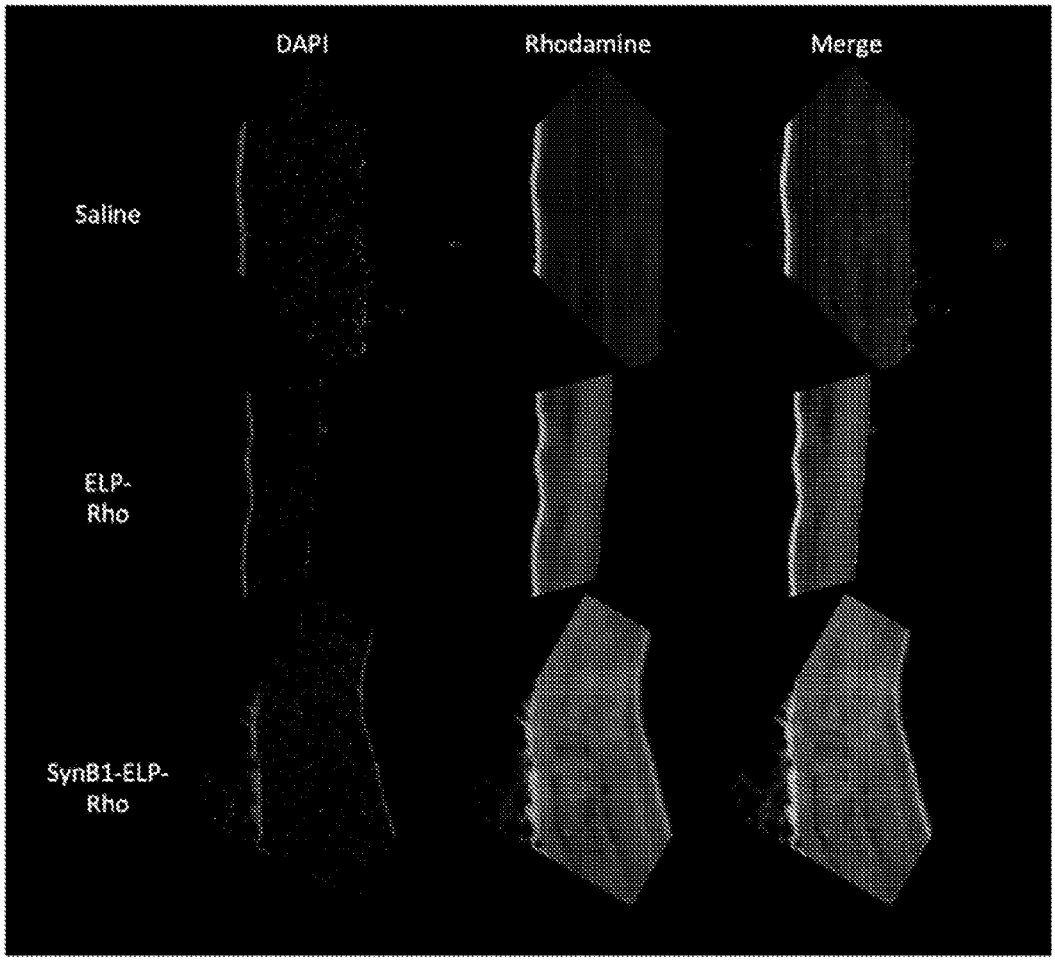

Figure 5

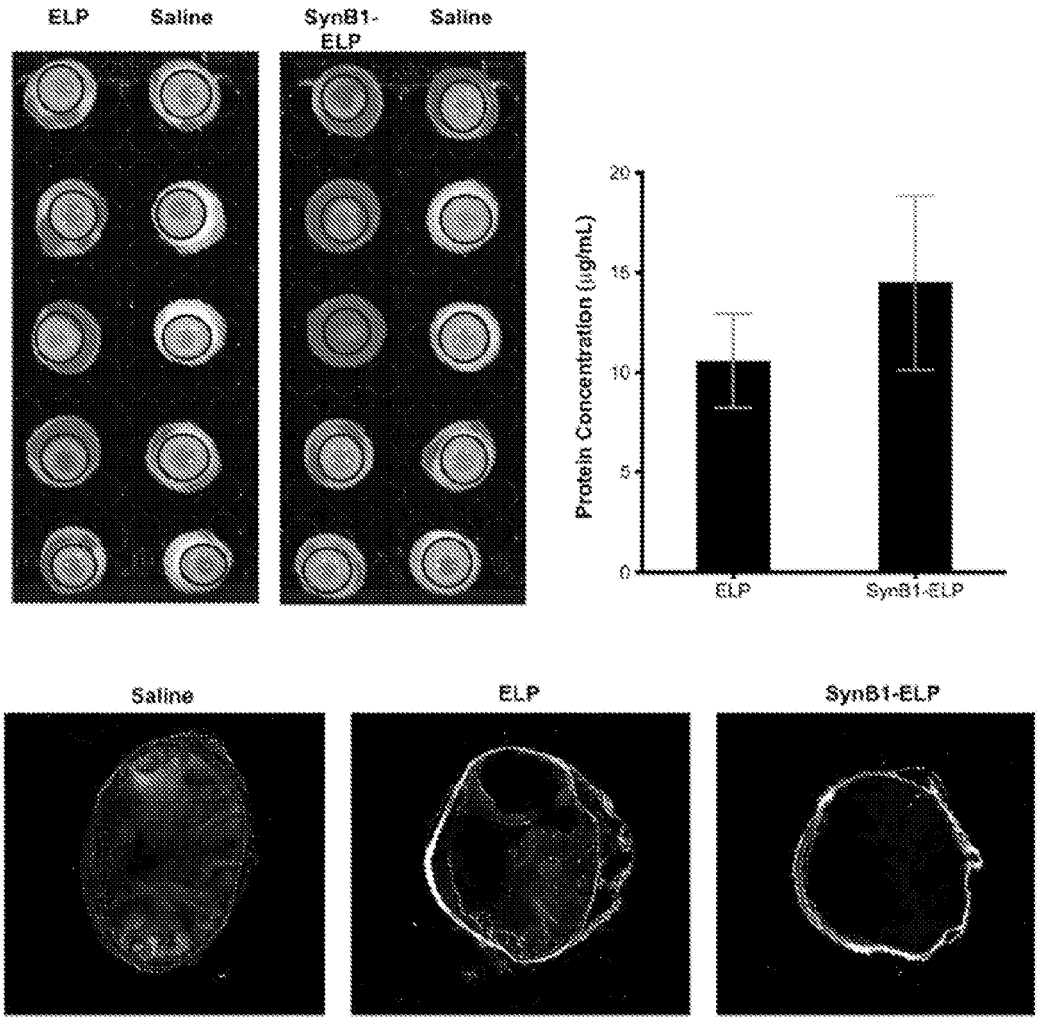

Figure 6

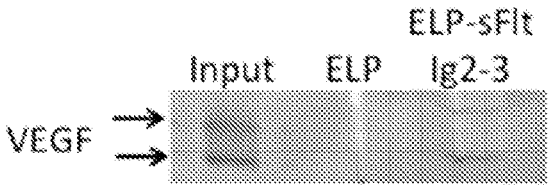

Figure 7

OCULAR COMPOSITIONS AND METHODS THEREOF

RELATED APPLICATIONS

[0001] This application claims priority from U.S. Provisional Application Ser. No. 61/985,808 filed Apr. 29, 2014, the entire disclosure of which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The presently-disclosed subject matter relates to compositions and methods for ocular delivery of therapeutic agents. In particular, the presently-disclosed subject matter relates to compounds comprising an elastic-like polypeptide (ELP) coupled to a therapeutic agent as well as compositions and methods thereof.

INTRODUCTION

[0003] Delivery of drugs to the eye via topical application is especially challenging. The corneal barrier consists of tight junction connected epithelial cells over a basement membrane layer that prevent the passage of large or hydrophilic molecules into the eye. Thus, treatment of numerous diseases and conditions that affect the eyes, including those for which therapeutic agents are available, can be difficult or impractical because there exists no simple and effective method for delivering therapeutic agents.

[0004] For instance, the cornea of the eye is normally an avascular environment, and maintenance of avascularity allows for optical clarity and acute vision. Both pro-angiogenic and anti-angiogenic proteins are expressed in the cornea, and maintenance of the avascular environment is dependent on a balance between them. A player in the maintenance of corneal avascularity is the expression of sFlt-1, a soluble isoform of the VEGF receptor which serves to naturally sequester VEGF. Inhibition of sFlt-1 expression is sufficient to abolish corneal avascularity in mice, but treatment is hampered by the lack of a system to deliver sFlt-1 to the eye.

[0005] On the other hand, corneal neovascularization (NV) is a pathological condition resulting from corneal injury or infection. Persistent pathological NV leads to development and accumulation of blood vessels that are immature and structurally weak, which can then lead to lipid exudation, inflammation, scarring, and ultimately, blindness. Current treatment strategies are limited to pharmacological interventions, such as steroids, NSAIDs, and anti-angiogenic growth factors, and surgical interventions, such as photodynamic therapy, laser ablation, cautery, and superficial keratectomy.

[0006] Similarly, bacterial keratitis can be a severe and sight threatening condition. Current therapy involves topical administration of antibiotics. However, this strategy is limited by poor penetration of many antibiotics into the cornea, rapid removal of the drugs by the natural formation of tears, and development of antibiotic resistance by the infecting bacteria.

[0007] Hence, there remains a need for compositions and treatment methods for administering therapeutic agents to the eye in simple, effective, and noninvasive manner.

SUMMARY

[0008] This summary describes several embodiments of the presently-disclosed subject matter, and in many cases, lists variations and permutations of these embodiments. This summary is merely exemplary of the numerous and varied embodiments. Mention of one or more representative features of a given embodiments is likewise exemplary. Such an embodiment can typically exist with or without the feature (s) mentioned; likewise, those features can be applied to other embodiments of the presently-disclosed subject matter, whether listed in this summary or not. To avoid excessive repetition, this summary does not list or suggest all possible combinations of such features.

[0009] The presently-disclosed subject matter relates to compositions and methods for ocular delivery of therapeutic agents. In particular, the presently-disclosed subject matter relates to compounds comprising an elastic-like polypeptide (ELP) coupled to a therapeutic agent as well as compositions and methods thereof.

[0010] In some embodiments of the presently-disclosed subject matter, a method of delivering a therapeutic agent to an eye is provided. In some embodiments, the method includes administering to the eye of a subject an effective amount of a compound that includes an elastin-like polypeptide (ELP) coupled to a therapeutic agent. In some embodiments, the ELP including at least one repeat of the amino acid sequence VPGXG (SEQ ID NO: 1). In some embodiments, non-limiting examples of administration methods includes topical administration, subconjunctival administration, intraocular injection. In some embodiments, the size of the ELP is configured to permit ocular penetration of the compound. In some embodiments, the ELP comprises about 5 to about 10 VPGXG sequences. In some embodiments, the ELP comprises about 10 to about 20 VPGXG sequences. In some embodiments, the ELP comprises about 20 to about 40 VPGXG sequences. In some embodiments, the ELP comprises about 40 to about 80 VPGXG sequences. In some embodiments, the X amino acid is hydrophilic which can permit stability of the compound in the ocular environment. In some embodiments, X includes Val, Ala, or Gly in a 1:8:7 ratio (e.g., SEQ ID NO:2). In some embodiments, X includes Val, Ala, or Gly in a 1:4:3 ratio (e.g., SEQ ID NO:3). In some embodiments, X includes Gly (e.g., SEQ ID NO:4). In some embodiments, X includes Ser (e.g., SEQ ID NO:5). In some embodiments, X includes His (e.g., SEQ ID NO:6). In some embodiments, X is hydrophobic to permit corneal penetration of the compound. In some embodiments, X includes Val (e.g., SEQ ID NO:7). In some embodiments, X includes Leu (e.g., SEQ ID NO:8). In some embodiments, X includes Ile (e.g., SEQ ID NO:9). In some embodiments, the therapeutic agent is linked to the ELP carrier with a cleavable linker to allow release of the therapeutic agent intraocularly.

[0011] In some embodiments of the presently disclosed subject matter, the compound further comprises a cell-penetrating peptide (CPP) coupled to the ELP. In some embodiments, the cell-penetrating peptide includes penetratin, Tat, SynB1, Bac, polyArg, MTS, Transportan, and pVEC. In some embodiments, the compound further includes an attachment site configured to couple to a therapeutic agent. In some embodiments, the attachment site includes one or more Cys residues at a N-terminus, a C-terminus, or an interior of the compound. In some

embodiments, the attachment site includes one or more Lys residues at a N-terminus, a C-terminus, or an interior of the compound.

[0012] In some embodiments of the presently disclosed subject matter, the compound forms a hydrogel after topical application or intraocular injection. In some embodiments, the compound has a phase transition below the ocular temperature, wherein ocular injection or application induces phase transfer and hydrogel formation. In some embodiments, the hydrogel formation increases ocular residence time and bioavailability of the therapeutic.

[0013] In some embodiments, the presently disclosed subject matter provides a method of treating a neovascularization disorder in a subject. The method includes administering to the eye of the subject an effective amount of a compound that comprises an elastin-like polypeptide (ELP) coupled to a therapeutic agent. In some embodiments, the ELP comprises at least one repeat of the amino acid sequence VPGXG (SEQ ID NO: 1). In some embodiments, the therapeutic agent is a VEGF antagonist. In some embodiments, the therapeutic agent is a member of the sFlt-1 family, a portion of the sFlt-1 protein (e.g., SEQ ID NO:10), or a combination thereof. In some embodiments, the therapeutic agent is sFlt-1 Ig-like domains 1, 2, and 3 (SEQ ID NO:11). In some embodiments, the therapeutic agent is sFlt-1 Ig-like domains 2 and 3 (SEQ ID NO:12). In some embodiments, the therapeutic agent comprises PEDF (SEQ ID NO:13). In some embodiments, the therapeutic agent comprises an anti-inflammatory drug, an anti-inflammatory peptide, or a combination thereof. In some embodiments, the method further comprises a cell-penetrating peptide. In some embodiments, non-limiting examples of the cell penetrating peptide are penetratin, Tat, SynB1, Bac, polyArg, MTS, Transportan, POD, and pVEC.

[0014] Further provided in some embodiments of the presently disclosed subject matter, is a method of treating an ocular infection in a subject. The method includes administering to the eye of a subject an effective amount of a compound that includes an elastin-like polypeptide (ELP) coupled to a therapeutic agent. In some embodiments, the ELP includes at least one repeat of the amino acid sequence VPGXG (SEQ ID NO: 1). In some embodiments, the therapeutic agent includes a BLP-1 peptide (SEQ ID NO:14). In some embodiments, the therapeutic agent includes a parasin-1 peptide (SEQ ID NO:15). In some embodiments, the therapeutic agent includes a magainin-2 peptide (SEQ ID NO:16). In some embodiments, the therapeutic agent includes a ranalexin peptide (SEQ ID NO:17). In some embodiments, the method further includes a cell-penetrating peptide. In some embodiments, non-limiting examples of the cell-penetrating peptide includes penetratin, Tat, SynB1, Bac, polyArg, MTS, Transportan, POD, and pVEC.

[0015] The presently disclosed subject matter, in some embodiments, further provides a composition. The composition includes a compound that includes an elastin-like polypeptide (ELP) coupled to a therapeutic agent, wherein the ELP comprises at least about 5 repeats of the amino acid sequence VPGXG (SEQ ID NO: 1), and a pharmaceutically acceptable carrier for topical delivery to an eye. In some embodiments, the composition includes eye drops, an ointment, or a combination thereof. In some embodiments, the composition further includes thickening agents. In some embodiments, the thickening agents includes polyvinyl alcohol, polyethylene glycol, methyl cellulose, and/or carboxymethyl cellulose. In some embodiments, the composition further includes an agent modulating tonicity. In some embodiments, the tonicity modulating agent includes boric acid and/or sodium phosphate buffer. In some embodiments, the composition further includes a surfactant to increase corneal penetration. In some embodiments, the surfactant includes benzalkonium chloride, polysorbate 20, polysorbate 80, and/or dioctyl sodium sulpho succinate. In some embodiments, the composition further includes a buffering agent to adjust the pH of the solution. In some embodiments, the ELP comprises about 5 to about 80 VPGXG sequences. In some embodiments, the X amino acid is hydrophilic and/or hydrophobic. In some embodiments, X includes one or more of Val, Ala, and Gly in a 1:8:7 ratio (e.g., SEQ ID NO:2), Val, Ala, and Gly in a 1:4:3 ratio e.g., (SEQ ID NO:3), Gly (e.g., SEQ ID NO:4), Ser (e.g., SEQ ID NO:5), His (e.g., SEQ ID NO:6), Val (e.g., SEQ ID NO:7), Leu (e.g., SEQ ID NO:8), Ile (e.g., SEQ ID NO:9), or a combination thereof. In some embodiments, the compound further comprises a cell-penetrating peptide (CPP) coupled to the ELP. Non-limiting examples of the cell-penetrating peptide includes penetratin, Tat, SynB1, Bac, polyArg, MTS, Transportan, POD, and pVEC. In some embodiments, the compound further comprises an attachment site configured to couple to a therapeutic agent. In some embodiments, the attachment site includes one or more Cys residues. In some embodiments, the attachment site includes one or more Lys residues. In some embodiments, the attachment site includes one or more Cys residues and one or more Lys residues. Non-limiting examples of the therapeutic agent include a VEGF antagonist, a member of the sFlt-1 family, a portion of the sFlt-1 protein (SEQ ID NO:10), sFlt-1 Ig-like domains 1, 2, and 3 (SEQ ID NO:11), PEDF (SEQ ID NO:13), an anti-inflammatory drug and/or peptide, a BLP-1 peptide (SEQ ID NO:14), a parasin-1 peptide (SEQ ID NO:15), a magainin-2 peptide (SEQ ID NO:16), and a ranalexin peptide (SEQ ID NO:17).

[0016] The presently disclosed subject matter, in some embodiments, provides a compound. In some embodiments, the compound includes an elastin-like polypeptide (ELP) coupled to a therapeutic agent, wherein the ELP comprising at least one repeat of the amino acid sequence VPGXG (SEQ ID NO: 1). In some embodiments, the ELP is about 16 to about 160 VPGXG (SEQ ID NO: 1) sequences. In some embodiments, the X amino acid is hydrophilic. In some embodiments, the X amino acid is hydrophobic. In some embodiments, the X amino acid is hydrophilic, hydrophobic, or a combination thereof. In some embodiments, X includes one or more of Val, Ala, and Gly in a 1:8:7 ratio (e.g., SEQ ID NO:2), Val, Ala, and Gly in a 1:4:3 ratio (e.g., SEQ ID NO:3), Gly (e.g., SEQ ID NO:4), Ser (e.g., SEQ ID NO:5), His (e.g., SEQ ID NO:6), Val (e.g., SEQ ID NO:7), Leu (e.g., SEQ ID NO:8), Ile (e.g., SEQ ID NO:9), or any combination thereof. In some embodiments, the compound further comprises a cell-penetrating peptide (CPP) coupled to the ELP. Non-limiting examples of the cell-penetrating peptide include penetratin, Tat, SynB1, Bac, polyArg, MTS, Transportan, POD, and pVEC. In some embodiments, the compound further comprises an attachment site configured to couple to a therapeutic agent. In some embodiments, the attachment site is one or more Cys residues. In some embodiments, the attachment site is one or more Lys residues. In some embodiments, the attachment site is one or

more Cys residues and one or more Lys residues. In some embodiments, the therapeutic agent includes one or more of a VEGF antagonist, a member of the sFlt-1 family, a portion of the sFlt-1 protein (SEQ ID NO:10), sFlt-1 Ig-like domain 1, 2, and 3 (SEQ ID NO:11), PEDF (SEQ ID NO:13), an anti-inflammatory drug and/or peptide, a BLP-1 peptide (SEQ ID NO:14), a parasin-1 peptide (SEQ ID NO:15), a magainin-2 peptide (SEQ ID NO:16), and a ranalexin peptide (SEQ ID NO:17).

BRIEF DESCRIPTION OF THE SEQUENCE, LISTING

[0017] SEQ ID NO:1 is an amino acid sequence, VPGXG, where X can be any amino acid except proline.

[0018] SEQ ID NO: 2 is a ELP, including a series of VPGXG (SEQ ID NO:1) units in which X is Val, Ala, and Gly in 1:8:7 ratio; SEQ ID NO: 2 can be repeated in a single ELP from 1 to about 10 times (n is 1 to about 10).

[0019] SEQ ID NO: 3 is a ELP, including a series of VPGXG (SEQ ID NO:1) units in which X is Val, Ala and Gly in 1:4:3 ratio; SEQ ID NO: 3 can be repeated in a single ELP from about 1 to about 20 times (n is 1 to about 20).

[0020] SEQ ID NO: 4 is a ELP sequence of about 8 to about 160 repeats of amino acid sequence $(VG\ VPGGG\ VPG)_n$, where n is about 8 to about 160.

[0021] SEQ ID NO: 5 is a ELP sequence of about 8 to about 160 repeats of amino acid sequence $(VG\ VPGSG\ VPG)_n$, where n is about 8 to about 160.

[0022] SEQ ID NO: 6 is a ELP sequence of about 8 to about 160 repeats of amino acid sequence $(VG\ VPGHG\ VPG)_n$, where n is about 8 to about 160.

[0023] SEQ ID NO: 7 is a ELP sequence of about 8 to about 160 repeats of amino acid sequence $(VG\ VPGVG\ VPG)_n$, where n is about 8 to about 160.

[0024] SEQ ID NO: 8 is a ELP sequence of about 8 to about 160 repeats of amino acid sequence $(VG\ VPGLG\ VPG)_n$, where n is about 8 to about 160.

[0025] SEQ ID NO: 9 is a ELP sequence of about 8 to about 160 repeats of amino acid sequence $(VG\ VPGIG\ VPG)_n$, where n is about 8 to about 160.

[0026] SEQ ID NO: 10 is an amino acid sequence of sFlt-1 protein.

[0027] SEQ ID NO: 11 is an amino acid sequence of sFlt-1 Ig-like domains 1, 2 and 3.

[0028] SEQ ID NO: 12 is an amino acid sequence of sFlt-1 Ig-like domains 2 and 3.

[0029] SEQ ID NO: 13 is an amino acid sequence of PEDF.

[0030] SEQ ID NO: 14 is an amino acid sequence of BLP-1 peptide.

[0031] SEQ ID NO: 15 is an amino acid sequence of parasin-1 peptide.

[0032] SEQ ID NO: 16 is an amino acid sequence of magainin-2 peptide.

[0033] SEQ ID NO: 17 is an amino acid sequence of a ranalexin peptide.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] FIG. **1** illustrates uptake of Proteins in Corneal Epithelial Cells. HCE cells were exposed to 10 μM fluorescently labeled ELP, SynB1-ELP, or Tat-ELP. 24 h after exposure, protein levels were determined by flow cytometry. Bars, sem.

[0035] FIG. **2** shows proliferation of Corneal Epithelial Cells after exposure to ELPs. HCE cells were exposed to the indicated concentration of ELP, SynB1-ELP, or Tat-ELP for 72 h. Cell survival was assessed using the MTS cell viability assay. Bars, sem.

[0036] FIG. **3** illustrates establishing the Rabbit Corneal Neovascularization model. NZW rabbits were anesthetized with isoflurane and topical proparacaine, and a corneal lesion was induced using a 60 sec application of silver nitrate. Blood vessel formation 7 days after lesioning is shown.

[0037] FIG. **4** shows ocular delivery of ELPs relative to IgG. A 3% solution of fluorescently labeled ELP, SynB1-ELP, Tat-ELP, or a non-specific IgG was applied topically to rabbit eyes 3 times over 6 hours. 2 h after the final administration, the eyes were removed and examined by ex vivo quantitative fluorescence to determine polypeptide levels.

[0038] FIG. **5** shows corneal penetration of ELP or SynB1-ELP. Rabbit eyes were harvested and rapidly frozen after exposure to 3 topical applications of 3% solutions of labeled proteins of a period of 6 hours. Eyes were cut into sagittal sections using a cryomicrotome, and sections were stained with DAPI to mark cell nuclei.

[0039] FIG. **6** shows ocular delivery of ELPs Following Increased Application Frequency. A 3% solution of fluorescently labeled ELP or SynB1-ELP was applied topically to rabbit eyes every 15 minutes for one hour, then every 30 minutes for five additional hours. 1 h after the final administration, the eyes were removed and examined by ex vivo quantitative fluorescence to determine polypeptide levels.

[0040] FIG. **7** shows ELP-sFlt Ig2-3 binding to ELP and ELP-sFlt Ig2-3 measured by SDS-PAGE and Western blot.

DESCRIPTION OF EXEMPLARY EMBODIMENTS

[0041] The details of one or more embodiments of the presently-disclosed subject matter are set forth in this document. Modifications to embodiments described in this document, and other embodiments, will be evident to those of ordinary skill in the art after a study of the information provided in this document. The information provided in this document, and particularly the specific details of the described exemplary embodiments, is provided primarily for clearness of understanding and no unnecessary limitations are to be understood therefrom. In case of conflict, the specification of this document, including definitions, will control.

[0042] The presently-disclosed subject matter includes compounds that can be utilized to administer a therapeutic agent to an eye of a subject. Embodiments of the compounds can cross the corneal barrier. Some embodiments can also penetrate and/or accumulate in the corneal stroma and other structures of the eye. In some embodiments the compounds comprise an elastin-like polypeptide (ELP) that is coupled to a therapeutic agent. Furthermore, in some embodiments the compound can further comprise a cell-penetrating peptide (CPP) coupled to the ELP. In some embodiments the present compounds can be utilized as a drug delivery vector that is capable of crossing the corneal barrier.

[0043] The terms "polypeptide", "protein", and "peptide", which are used interchangeably herein, refer to a polymer of the protein amino acids, or amino acid analogs, regardless of its size or function. Although "protein" is often used in reference to relatively large polypeptides, and "peptide" is

often used in reference to small polypeptides, usage of these terms in the art overlaps and varies. The term "polypeptide" as used herein refers to peptides, polypeptides, and proteins, unless otherwise noted. The terms "protein", "polypeptide", and "peptide" are used interchangeably herein when referring to a gene product. Thus, exemplary polypeptides include gene products, naturally occurring proteins, homologs, orthologs, paralogs, fragments and other equivalents, variants, and analogs of the foregoing. Furthermore, the term "fusion polypeptide" is used herein to generally refer to a polypeptide formed from two or more distinct polypeptides.

[0044] The term "therapeutic agent" and the like is used herein to refer to substances that can alter, inhibit, active, catalyze, or otherwise affect a biological or chemical event in a subject. In some embodiments a therapeutic agent has the effect of treating a disease, condition, or disorder in a subject, and possibly in the eye of a subject. Exemplary active agents include, but are not limited to, enzymes, organic catalysts, ribozymes, organometallics, proteins, glycoproteins, peptides, polyamino acids, antibodies, nucleic acids, steroidal molecules, antibiotics, antibacterial agents, anti-inflammatory agents, antivirals, antimycotics, anticancer agents, analgesic agents, antirejection agents, immunosuppressants, cytokines, carbohydrates, oleophobics, lipids, pharmaceuticals (i.e., drugs; including small molecules), chemotherapeutics, and combinations thereof.

[0045] In some instances the compound is for treating a neovascularization disorder, and the therapeutic agent includes one or more of VEGF antagonist, a member of the sFlt-1 family, a portion of the sFlt-1 protein (SEQ ID NO: 10), sFlt-1 Ig-like domain 1, 2, and 3 (SEQ ID NO:11), and PEDF (SEQ ID NO:13).

[0046] In this respect, the sFlt-1 protein is a splice variant of the VEGF receptor that consists of its soluble extracellar portion. sFlt is made up of 7 immunoglobulin-like (Ig) domains which are responsible for VEGF binding. The first three domains (sFlt Ig1-3) are capable of binding VEGF with an affinity 2-fold lower than the full length protein, and domains 2-3 (sFlt Ig2-3) can bind with 4.5-fold lower affinity than the full protein. Given the small size of the sFlt Ig1-3 and sFlt Ig2-3 domains, about 20 kDa and 30 kDa, respectively, and their high affinity for VEGF, compounds comprising therapeutic agents with such sFlt domains could be useful in topical applications for treatment of corneal neovascularization disorder.

[0047] Furthermore, the antibacterial agents can include antibacterial peptides, which are a class of naturally occurring short peptides that have bacteriocidal or bacteriostatic properties. They can be derived mostly from frogs and insects and the like, and some are found in cows and humans and the like. Antimicrobial peptides often have a positive charge and function by binding bacterial membranes and inducing pore formation or cell lysis. Antibacterial peptides are relatively less susceptible to induction of resistance in the target microorganisms. Exemplary antibacterial peptides include, but are not limited to, magainin-2, parasin-1, BLP-1, and ranalexin.

[0048] In some instances the compound is for treating a ocular infection, and the therapeutic agent includes one or more of BLP-1 peptide (SEQ ID NO:14), a parasin-1 peptide (SEQ ID NO:15), a magainin-2 peptide (SEQ ID NO:16), and a ranalexin peptide (SEQ ID NO:17).

[0049] In some embodiments, the compound includes reactive sites for attachment of therapeutic agents, with or without a cleavable linker. A non-limiting list of potential therapeutic agents that can be provided with the present compounds include those listed in the following tables.

TABLE 1

Partial list of pharmaceuticals that can be coupled to a ELP for delivery.
Ocular Pharmaceuticals

Ketorolac	Naphazoline	Lidocaine
Pemirolast	Brimonidine	Azelastine
Azithromycin	Bepotastine	Besifloxacin
Betaxon	Cosopt	Cysteamine
Difluprednate	Aflibercept	Tasimelteon
Ocriplasmin	Lotemax	Enoxaparin
Gatifloxacin	Bimatoprost	Pegaptanib
Ofloxacin	Dexamethasone	Levofloxacin
Unoprostone	Cyclosporine	Travoprost
Valganciclovir	Viroptic	Cidofovir
Verteporfin	Vitrasert	Vitravene
Zaditor	Tafluprost	Ganciclovir
Dexamethasone	Fluocinolone	Loteprednol
Difluprednate	Fluoromethalone	Prednisolone
Medrysone	Triamcinolone	Rimexolone

TABLE 2

Partial list of peptide, protein, and antibody therapeutic agents that can be coupled to a ELP for delivery.

Peptide Name	Protein of origin	Amino Acids
THERAPEUTIC PEPTIDES		
PNC-2	Ras	96-110
PNC-7	Ras	35-47
PNC-25	SOS	994-1004
n.s.*	Raf	97-110
n.s.*	Raf	143-150
n.s.*	NF1-GAP	1121-1128
SP1068	EGFR	1063-1073
SY317	Shc	312-323
n.s.*	MEK1	1-13
n.s.*	GST-pi	34-50
JNKI1	JIP1/IB1	153-172
JNKI2	JIP2/IB2	134-151
I-JIP	JIP1/IB1	143-163
TI-JIP	JIP1/IB1	153-163
NBD	IKKβ	735-745
CC2	NEMO	253-287
LZ	NEMO	294-336
SN50	NF-κB p50	360-369
pp21	IκBα	21-41
p65-P1	NF-κB p65	271-282
p65-P6	NF-κB p65	525-537
C1	p53	369-383
Peptide 46	p53	361-382
CDB3	53BP2	490-498
TIP	p53	12-30
Super-TIP	(phage selected)	
PNC-27	p53	12-26
PNC-21	p53	12-20
PNC-28	p53	17-26
αHDM2	p53	16-27
Peptide 3	p14ARF	1-20
H1-S6A, F8A	c-Myc	368-381
n.s.*	p21	17-33
n.s.*	p21	63-77
Peptide 10	p21	141-160
W10	p21	139-164
Peptide 6	p16	84-103
Peptide 5a	p27	Modified from 30-34

TABLE 2-continued

Partial list of peptide, protein, and antibody therapeutic agents that can be coupled to a ELP for delivery.

Peptide Name	Protein of origin	Amino Acids
C4	cyclin A	285-306
n.s.*	E2F	87-64
n.s.*	Rb	864-880
Akt-in	TCL1	10-24
Peptide2	FKHRL1	16-24
n.s.*	Bak	72-87
TO4	Bax	52-72
n.s.*	Bax	53-86
n.s.*	Bad (*mus musculis*)	140-165
n.s.*	Bad	103-127
BH3 BAD	Bad	103-123
Bim	Bim	145-165
n.s.*	Bid	84-99
$SAHB_A$	Bid	80-101
Smac-7	Mature Smac	1-7
n.s.*	Mature Smac	1-4
dAVPI	Mature Smac	1-4
Nox2ds	NADPH oxidase 2	86-94
Nox2 C-terminal peptide 1	NADPH oxidase 2	552-570
Nox2 C-terminal peptide 2	NADPH oxidase 2	550-569
Nox2 C-terminal peptide (with mutation at residue 500)	NADPH oxidase 2	491-504
$p22^{phox}$ derived peptide 1	$p22^{phox}$	9-23
$p22^{phox}$ derived peptide 2	$p22^{phox}$	31-45
$p22^{phox}$ derived peptide 3	$p22^{phox}$	47-61
$p22^{phox}$ derived peptide 4	$p22^{phox}$	85-99
$p22^{phox}$ derived peptide 5	$p22^{phox}$	113-127
$p22^{phox}$ derived peptide 6	$p22^{phox}$	82-95
$p22^{phox}$ derived peptide 7	$p22^{phox}$	175-194
$p47^{phox}$ derived peptide 1	$p47^{phox}$	323-332
$p47^{phox}$ derived peptide 2	$p47^{phox}$	314-331
$p47^{phox}$ derived peptide 3	$p47^{phox}$	315-328
$p47^{phox}$ derived peptide 4	$p47^{phox}$	323-332
$p47^{phox}$ derived peptide 5	$p47^{phox}$	334-347
Antibacterial Peptide Classes		
Defensins	Protegrins	Tachyplesins
Brevinins	Indolicidin	PR-39
Magainins	Cecropins	Ranalexin
Dermaseptin	Bimbinin	Andropin
Sarcotoxin	Sapecin	Apidaecin
Abaecin	Hymenoptaecin	Bee defensin
Mellitin	Attacins	Bactenecin
THERAPEUTIC PROTEINS		
VEGF	Insulin	β-Gluco-cerebrosidase
PIGF	Growth hormone	Alglucosidase-α
IL10	Mecasermin	Laronidase
IL11	Factor VIII	Idursulphase
Erythropoietin	Factor IX	Galsulphase
Darbepoetin	Antithormbin III	Agalsidase-β
G-CSF	Protein C	α-1-Proteinase inhibitor
Peg-G-CSF	tPA	Lipase
GM-CSF	Urokinase	Amylase
α-interferon	Factor VIIa	Adenosine deaminase
Interferon-α2a	Calcitonin	Albumin
Interferon-α2b	Teriparatide	FSH
Peg-Interferon-α2a	Exenatide	HCG
Peg-Interferon-α2b	Octreotide	Lutropin
Interferon-αN3	rhBMP2	Nesiritide
Interferon-β1a	rhBMP7	Botulinum Toxin type A
Interferon-β1b	GnRH	Botulinum Toxin type B
Interferon-γ1b	KGF	Collagenase
IL2	PDGF	DNAse I
ETAF	Trypsin	Hyaluronidase
Peg-Asparaginase	Bivalirudin	Papain
Rasbuicase	Streptokinase	L-Asparaginase
Lepirudin	Anistreplase	

TABLE 2-continued

Partial list of peptide, protein, and antibody therapeutic agents that can be coupled to a ELP for delivery.

Peptide Name	Protein of origin	Amino Acids
ANTIBODIES		
Bevacizumab	Abatacept	Basiliximab
Cetuximab	Anakinra	Daclizumab
Panitumumab	Adalimumab	Muromonab-CD3
Alemtuzumab	Etanercept	Omalizumab
Rituximab	Infliximab	Palivizimuab
Trastuzumab	Alefacept	Enfuvirtide
Ranibuzumab	Efalizumab	Abciximab
Denileukin diftitox	Natalizumab	Pegvisomant
Ibritumomab tiuxetan	Eculizumab	GHRH
Gemtuzumab ozogamicin	DPPD	Secretin
Tositumomab	Glucagon	TSH
Capromab pendetide	Indium-111-ocreotide	Satumomab pendetide
Arcitumomab	Nofetumomab	Apcitide
Imciromab pentetate	Technetium fanolesomab	Ranibizumab

*n.s., name not specified

[0050] The ELP in some embodiments refers to a polypeptide comprised of at least one repeat of the amino acid sequence VPGXG, wherein X can be any amino acid except for proline (SEQ ID NO: 1). In other embodiments ELP can be of a size that permits ocular penetration of the compound, and in certain embodiments is small enough to permit ocular penetration. In some embodiments the ELP is hydrophilic so as to increase the residence time of the compound in the ocular environment, thereby increasing its stability in the ocular environment. In some embodiments the ELP and/or X is hydrophobic to permit corneal penetration of the compound. In some embodiments the ELP and/or X may have a combination of the properties described herein. For example, the ELP can comprise a hydrophilic portion and a hydrophobic portion.

[0051] Some embodiments of compounds include, but are not limited to, ELP that includes about 5, about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, or about 80 VPGXG sequences. In some embodiments the ELP will include about 5 to about 10 VPGXG sequences, about 10 to about 20 VPGXG sequences, about 20 to about 40 VPGXG sequences, or about 40 to about 80 VPGXG sequences.

[0052] In yet other embodiments, the ELP of the present compounds are such that X includes Val, Ala, or Gly in a 1:8:7 ratio (SEQ ID NO:2) or such that X includes Val, Ala, or Gly in a 1:4:3 ratio (SEQ ID NO:3). In certain embodiments X includes Gly (SEQ ID NO:4). In certain embodiments X includes Ser (SEQ ID NO:5). In certain embodiments X includes His (SEQ ID NO:6). In certain embodiments X includes Val (SEQ ID NO:7). In certain embodiments X includes Leu (SEQ ID NO:8). In certain embodiments X includes Ile (SEQ ID NO:9).

[0053] In some embodiments, the ELP of the present compounds form transparent hydrogels on the surface of the eye or when injected into or around the eye in order to increase residence time and attain controlled release of therapeutics.

[0054] ELP is a macromolecular carrier that has several advantages. It can be an inert and biodegradable macromolecule, giving it a good pharmacokinetic profile and very low

immunogenicity. Also, as opposed to chemically synthesized polymers, ELP can be expressed in and easily purified from *E. coli*. The ELP sequence can be manipulated, thereby making it relatively simple to generate chimeras of ELP fused to therapeutic agents, such as peptides. The ELP fusion can also be protease resistant and non-immunogenic, providing protection for the fused cargo from degradation and immunogenicity in vivo.

[0055] Embodiments of the presently-disclosed compounds can possess advantages by virtue of comprising ELP. In some instances ELP increases the solubility the therapeutic agents. In some instances ELP can protect labile therapeutic agents from degradation in vivo. Peptides, for instance, can be prone to degradation in blood plasma and in tissues in vivo. ELP can protect certain therapeutic, agents from enzymatic degradation. In some instance ELP fusion can decrease the immunogenicity of therapeutic agents.

[0056] As described herein ELP can also be modified relatively easily to carry a therapeutic agent, such as a protein, and/or to incorporate attachment sites for coupling (i.e., binding) of therapeutic agents, such as small molecules. ELP can also be purified after recombinant expression in bacteria.

[0057] In some instances, the present compounds include an ELP that is targeted to desired tissues. For example, in some embodiments ELP and/or the compound can include a targeting agent that selectively binds and/or is attracted to a targeting substance. Target agents can include, but are not limited to, peptides, proteins, small molecules, and antibodies. In some instances the targeting agent is a CPP that can increase cell and tissue uptake, direct ELP to specific tissues, direct ELP to specific intracellular compartments, or a combination thereof.

[0058] As mentioned above, the presently-disclosed subject matter includes compounds that include an ELP coupled to a therapeutic agent, and that further comprise a cell-penetrating peptide (CPP). In some embodiments a fusion polypeptide is comprised of the ELP, the CPP, and, optionally, the therapeutic agent. Exemplary CPPs utilized in the present compounds include, but are not limited to penetratin, Tat, SynB1, Bac, polyArg, MTS, Transportan, pVEC, and peptide for ocular delivery (POD).

[0059] Some embodiments of the present compounds further include an attachment site configured to couple (e.g., electrostatically and/or covalently bind) to a therapeutic agent. In some embodiments a compounds comprises a plurality of attachment sites for one or more types of therapeutic agents. In some embodiments the attachment site includes one or more Cys residues at a N-terminus, a C-terminus, or an interior of the compound. In some embodiments the attachment site includes one or more Lys residues at a N-terminus, a C-terminus, or an interior of the compound.

[0060] The presently-disclosed subject matter includes kits comprising a compound, as disclosed herein, packaged together with a therapeutic agent. The compound can include any of the compounds described herein. The therapeutic agent can also include any of the therapeutic agents described herein. In some embodiment the kit provides a compound that includes an ELP as well as a therapeutic agent. In some embodiments the kit provides a compound that includes an ELP and a CPP as well as a therapeutic agent. The compound and therapeutic agent provided in the kit can be bound by known means before administration to a subject in need thereof. In some embodiments the kit includes two or more different therapeutic agents.

[0061] The presently-disclosed subject matter also includes compositions that comprise a compound that includes an elastin-like polypeptide (ELP) coupled to a therapeutic agent, the ELP including at least about 5 repeats of the amino acid sequence VPGXG (SEQ ID NO: 1), and that further comprise a pharmaceutically acceptable carrier for topical delivery to an eye.

[0062] The term "pharmaceutically acceptable carrier" refers to sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, as well as sterile powders for reconstitution into sterile solutions or dispersions just prior to use. These compositions can also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms can be ensured by the inclusion of various antibacterial and antifungal agents such as paraben, chlorobutanol, phenol, sorbic acid and the like. It can also be desirable to include isotonic agents such as sugars, sodium chloride and the like. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. The formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable media just prior to use. As discussed herein, the pharmaceutically acceptable carriers can include drop solutions for topical administration to the eye of a subject.

[0063] The presently-disclosed subject matter further includes a method of using the compounds described herein. In some embodiments the method comprise delivering a therapeutic agent to an eye. In specific embodiments the method comprises administering to the eye of a subject an effective amount of a compound that includes an elastin-like polypeptide (ELP) coupled to a therapeutic agent, the ELP including at least one repeat of the amino acid sequence VPGXG (SEQ ID NO: 1). In other method any of the compounds and/or compositions described herein can be administered to an eye.

[0064] In this regard, the term "administer" refers to any method of providing a compound or composition thereof to a subject. Such methods are well known to those skilled in the art and include, but are not limited to, topical administration, subconjunctival administration, intraocular injection, including intraocular injection into the aqueous or vitreous humor, and the like. In some embodiments administer refers to administration via the eye of a subject, which can include topical administration by depositing a compound or composition thereof on or near the eye. In some embodiments administration can refer to administration via topical eye drops, ointments, or other compositions. Administration can be continuous or intermittent. In various aspects, a preparation can be administered therapeutically; that is, administered to treat an existing disease or condition. In further various aspects, a preparation can be administered prophylactically; that is, administered for prevention of a disease or condition.

[0065] In this respect, one problem that can be encountered with antibody therapy in the eye after intraocular injection is that the antibodies can get out of the eye. This treatment is sometimes used for macular degeneration, for example, despite its shortcoming. The antibodies can escape

the eye because they can be substrates for binding to the neonatal Fc receptor (FcRn), an antibody-binding protein expressed at the retinal—blood barrier that is responsible for active antibody transport across that barrier. However, because certain embodiments of the presently-disclosed compounds do not comprise an Fc domain, these embodiments do not bind FcRn and show lower or no systemic uptake after intraocular injection.

[0066] In some embodiments the method for administering the present compounds and compositions further include treating a disease or condition in the subject. The terms "treatment" or "treating" refer to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder.

[0067] Exemplary conditions and diseases that can be treated by certain methods include, but are not limited to, corneal diseases such as corneal neovascularization and keratitis, diseases of the soft tissue surrounding the eye, and diseases of the posterior eye such as macular degeneration, including wet macular degeneration. In other embodiments the disease or condition can include endophthalmitis, conjunctivitis, trachoma, periorbital cellulitis, contact-lens related infections, uveitis, *Streptococcus, Staphylococcus, Pseudomonas* infection, and the like. Other diseases and conditions include any that can be treated by a therapeutic agent that can be administered by the present compounds.

[0068] Furthermore, the term "subject" is inclusive of both human and animal subjects. Thus, veterinary uses are provided in accordance with the presently disclosed subject matter and the presently-disclosed subject matter provides methods for preventing oxidative damage in mammals such as humans, as well as those mammals of importance due to being endangered, such as Siberian tigers; of economic importance, such as animals raised on farms for consumption by humans; and/or animals of social importance to humans, such as animals kept as pets or in zoos. Examples of such animals include but are not limited to: carnivores such as cats and dogs; swine, including pigs, hogs, and wild boars; ruminants and/or ungulates such as cattle, oxen, sheep, giraffes, deer, goats, bison, and camels; and horses. Also provided is the treatment of birds, including the treatment of those kinds of birds that are endangered and/or kept in zoos, as well as fowl, and more particularly domesticated fowl, i.e., poultry, such as turkeys, chickens, ducks, geese, guinea fowl, and the like, as they are also of economic importance to humans. Thus, also provided is the treatment of livestock, including, but not limited to, domesticated swine, ruminants, ungulates, horses (including race horses), poultry, and the like.

[0069] In some embodiments the present compounds and compositions are administered by topical eye drops. In some embodiments the compounds can be detectable in other ocular structures, including the retina, after topical eye administration. The compounds can also accumulate in the corneal epithelium and penetrate to the stroma.

[0070] The presently-disclosed subject matter also includes methods for synthesizing the present compounds and compositions. In this respect, ELP is a thermally responsive polypeptide that can selectively form aggregates above a characteristic transition temperature (T_t). In some embodiments this thermally responsive nature can be exploited for purification of ELP-fused compounds by repeated centrifugation steps above and below the T_t, a process known as inverse transition cycling. In some embodiments, the T_t can be tuned to induce hydrogel formation when administered topically to the eye or injected into or around the eye.

[0071] The presently-disclosed subject matter is further illustrated by the following specific but non-limiting examples. The following examples may include compilations of data that are representative of data gathered at various times during the course of development and experimentation related to the present invention.

EXAMPLES

Example 1

[0072] This Example characterizes the uptake of elastic-like polypeptides (ELPs) and cell-penetrating peptide ELP fusion polypeptides (CPP-ELPs) in human corneal epithelial cells (HCEs). To determine if CPPs could mediate the uptake of ELP in corneal cells, HCEs grown in culture were exposed to 10 μM fluorescently-labeled ELP, SynB1-ELP, or Tat-ELP. After 24 h incubation with the labeled proteins, the cells were detached and analyzed by flow cytometry. The mean fluorescence intensity was determined for all cells, and the fluorescence value was corrected to account for differences in labeling efficiency among the proteins. As shown in FIG. **1**, ELP was detectable over autofluorescence in HCE cells, and the cellular uptake was increased 2.8-fold and 3.9-fold with SynB1 and Tat CPPs, respectively.

[0073] In addition to uptake efficiency, toxicity of ELP or CPP-ELPs to HCE cells was examined. Cells were exposed to varying concentrations of ELP, SynB1-ELP, or Tat-ELP for 72 hours, and cell number was determined using the MTS cell proliferation assay. As shown in FIG. **2**, ELP and SynB1-ELP had no detectable toxicity to HCE cells at concentrations up to 40 μM. In contrast, Tat-ELP did inhibit HCE cell proliferation with an IC50 between 10 and 20 μM. These data indicate that the ELP carrier, and some CPP-ELPs, are non-toxic to corneal epithelial cells and good candidates for corneal drug delivery. They also demonstrate that some CPPs have toxicity to corneal cells, and prediction of toxicity is not possible a priori. Therefore, each candidate drug delivery vector must be made and tested individually.

Example 2

[0074] This Example characterizes the development of a rabbit corneal neovascularization (CN) model. Rabbits were chosen for this model because the thickness of their corneal epithelial layer is similar to that of humans. New Zealand white rabbits were anesthetized with isoflurane, and a corneal burn was induced using a 60 second application of a

silver nitrate cautery stick. As shown in FIG. **3**, 7 days after corneal injury, the rabbits developed a neovascular response in the injured eye.

Example 3

[0075] This Example characterizes penetration of the corneal barrier by ELP and CPP-ELPs, and compares ELP corneal accumulation to a model antibody, immunoglobulin. G (IgG). Fluorescently labeled ELP, SynB1-ELP, Tat-ELP, or IgG was applied topically via eye drops three times over 6 h in rabbits. The contralateral eye was administered saline control. 8 h after the first application, the animals were sacrificed and the eyes removed for ex vivo analysis. As shown in FIG. **4**, ELP accumulated in the rabbit cornea at levels over seven-fold higher than IgG. SynB1-ELP and Tat-ELP also accumulated in the cornea much more efficiently than IgG, but the CPP-ELP corneal levels were not enhanced relative to ELP control.

[0076] After total fluorescence analysis, the eyes were frozen and cut using a cryomicrotome. Sagittal sections were used in order to visualize the cornea in cross-section. Sections were stained with DAPI to mark cell nuclei and imaged with an epifluorescence microscope. As shown in FIG. **5**, the epithelial layer was brightly autofluorescent, but very little fluorescence was seen in the stroma in saline treated eyes. In contrast, both ELP and SynB1-ELP penetrated through the corneal epithelium and into the stroma. Without being bound by theory or mechanism, other CPPs may enhance the penetration of the polypeptides.

[0077] Thus, the ELP and CPP-ELP drug vectors can be effective for delivery of agents through the corneal barrier and into the stroma, the site of neovascular development.

[0078] The frequency of dosing was increased to further test the corneal uptake and penetration of ELP and SynB1-ELP. The proteins were applied topically every 15 minutes for one hour, then every 30 minutes for five additional hours. One hour after the last application, the eyes were removed for ex vivo fluorescence analysis. As shown in FIG. **6**, both ELP and SynB1-ELP accumulated in the cornea at levels much higher than autofluorescence control. SynB1-ELP levels were slightly higher than ELP levels using this dosing regimen, but the differences were not statistically significant. Eyes were also cryosectioned to examine the distribution around the eye after topical administration. This analysis revealed that both ELP and SynB1-ELP distribute around the entire eye after topical administration, and they both penetrate the corneal barrier as well as the sclera and retina. This analysis highlights the potential for using ELP-based carriers for delivery of therapeutics to all parts of the eye for treatment of many ocular disorders.

Example 4

[0079] This Example ELP-fused sFlt Ig compounds binding to VEGF. ELP-sFlt fusion proteins were made by recombinant expression in *E. coli*. As a preliminary test to insure that the sFlt Ig domain could still bind VEGF when fused to the ELP carrier, in vitro pulldown assay was performed. ELP-sFlt Ig2-3 or an ELP control lacking the sFlt peptide were incubated with purified VEGF for 1 h at 37° C. in physiological saline. Thermal precipitation of ELP and centrifugation were used to pull down ELP or ELP-sFlt Ig2-3, and the thermal precipitation was carried out two times to remove any remaining unbound protein. The precipitated proteins were separated by SDS-PAGE, transferred to nitrocellulose membranes, and the membranes were probed for VEGF by Western blot. As shown in FIG. **7**, ELP-sFlt Ig2-3 was able to pull down VEGF, but the control ELP lacking the sFlt peptide did not. These results show that the sFlt peptide can maintain its ability to bind VEGF when fused to ELP.

[0080] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the presently-disclosed subject matter belongs. Although any methods, devices, and materials similar or equivalent to those described herein can be used in the practice or testing of the presently-disclosed subject matter, representative methods, devices, and materials are now described.

[0081] Following long-standing patent law convention, the terms "a", "an", and "the" refer to "one or more" when used in this application, including the claims. Thus, for example, reference to "a cell" includes a plurality of such cells, and so forth.

[0082] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about". Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and claims are approximations that can vary depending upon the desired properties sought to be obtained by the presently-disclosed subject matter.

[0083] As used herein, the term "about," when referring to a value or to an amount of mass, weight, time, volume, concentration or percentage is meant to encompass variations of in some embodiments ±20%, in some embodiments ±10%, in some embodiments ±5%, in some embodiments ±1%, in some embodiments ±0.5%, and in some embodiments ±0.1% from the specified amount, as such variations are appropriate to perform the disclosed method.

[0084] As used herein, ranges can be expressed as from "about" one particular value, and/or to "about" another particular value. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as "about" that particular value in addition to the value itself. For example, if the value "10" is disclosed, then "about 10" is also disclosed. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

[0085] Throughout this document, various references are mentioned. All such references are incorporated herein by reference, including the references set forth in the following list:

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INCORPORATION BY REFERENCE

[0149] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

[0150] It will be understood that various details of the presently disclosed subject matter can be changed without departing from the scope of the subject matter disclosed herein. Furthermore, the foregoing description is for the purpose of illustration only, and not for the purpose of limitation.

SEQUENCE LISTING

SEQ ID NO: 1
VPGXG
wherein X comprises an amino acid and does not include proline

SEQ ID NO: 2
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wherein n is about 1 to about 10

SEQ ID NO: 3
(VG VPGAG VPGGG VPGAG VPGGG VPGAG VPGGG VPGAG VPG)$_n$
wherein n is about 1 to about 20

SEQ ID NO: 4
(VG VPGGG VPG)$_n$
wherein n is about 8 to about 160

-continued

SEQUENCE LISTING

SEQ ID NO: 5
(VG VPGSG VPG)$_n$
wherein n is about 8 to about 160

SEQ ID NO: 6
(VG VPGHG VPG)$_n$
wherein n is about 8 to about 160

SEQ ID NO: 7
(VG VPGVG VPG)$_n$
wherein n is about 8 to about 160

SEQ ID NO: 8
(VG VPGLG VPG)$_n$
wherein n is about 8 to about 160

SEQ ID NO: 9
(VG VPGIG VPG)$_n$
wherein n is about 8 to about 160

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SEQUENCE LISTING

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SEQ ID NO: 15
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SEQUENCE LISTING

SEQ ID NO: 16
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SEQ ID NO: 17
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SEQUENCE LISTING

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about 8 to about 160

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Glu Leu Ser Leu Lys Gly Thr Gln His Ile Met Gln Ala Gly Gln Thr
35 40 45

Leu His Leu Gln Cys Arg Gly Glu Ala Ala His Lys Trp Ser Leu Pro
50 55 60

Glu Met Val Ser Lys Glu Ser Glu Arg Leu Ser Ile Thr Lys Ser Ala
65 70 75 80

Cys Gly Arg Asn Gly Lys Gln Phe Cys Ser Thr Leu Thr Leu Asn Thr
85 90 95

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    130                 135                 140

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145                 150                 155                 160

Thr Ser Pro Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp Thr
                165                 170                 175

Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe
            180                 185                 190

Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu
        195                 200                 205

Ala Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg
    210                 215                 220

Gln Thr Asn Thr Ile Ile Asp Val Gln Ile Ser Thr Pro Arg Pro Val
225                 230                 235                 240

Lys Leu Leu Arg Gly His Thr Leu Val Leu Asn Cys Thr Ala Thr Thr
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Pro Leu Asn Thr Arg Val Gln Met Thr Trp Ser Tyr Pro Asp Glu Lys
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        275                 280                 285

Ala Asn Ile Phe Tyr Ser Val Leu Thr Ile Asp Lys Met Gln Asn Lys
    290                 295                 300

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Ser Val Asn Thr Ser Val His Ile Tyr Asp Lys Ala Phe Ile Thr Val
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Tyr Arg Leu Ser Met Lys Val Lys Ala Phe Pro Ser Pro Glu Val Val
        355                 360                 365

Trp Leu Lys Asp Gly Leu Pro Ala Thr Glu Lys Ser Ala Arg Tyr Leu
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Thr Arg Gly Tyr Ser Leu Ile Ile Lys Asp Val Thr Glu Glu Asp Ala
385                 390                 395                 400

Gly Asn Tyr Thr Ile Leu Leu Ser Ile Lys Gln Ser Asn Val Phe Lys
                405                 410                 415

Asn Leu Thr Ala Thr Leu Ile Val Asn Val Lys Pro Gln Ile Tyr Glu
            420                 425                 430

Lys Ala Val Ser Ser Phe Pro Asp Pro Ala Leu Tyr Pro Leu Gly Ser
        435                 440                 445

Arg Gln Ile Leu Thr Cys Thr Ala Tyr Gly Ile Pro Gln Pro Thr Ile
    450                 455                 460

Lys Trp Phe Trp His Pro Cys Asn His Asn His Ser Glu Ala Arg Cys
465                 470                 475                 480

Asp Phe Cys Ser Asn Asn Glu Glu Ser Ser Ile Leu Asp Ala Asp Ser
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Asn Met Gly Asn Arg Ile Glu Ser Ile Thr Gln Arg Met Ala Ile Ile
            500                 505                 510
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        515                 520                 525

Ile Ser Gly Ile Tyr Ile Cys Ile Ala Ser Asn Lys Val Gly Thr Val
    530                 535                 540

Gly Arg Asn Ile Ser Phe Tyr Ile Thr Asp Val Pro Asn Gly Phe His
545                 550                 555                 560

Val Asn Leu Glu Lys Met Pro Thr Glu Gly Glu Asp Leu Lys Leu Ser
                565                 570                 575

Cys Thr Val Asn Lys Phe Leu Tyr Arg Asp Val Thr Trp Ile Leu Leu
            580                 585                 590

Arg Thr Val Asn Asn Arg Thr Met His Tyr Ser Ile Ser Lys Gln Lys
        595                 600                 605

Met Ala Ile Thr Lys Glu His Ser Ile Thr Leu Asn Leu Thr Ile Met
    610                 615                 620

Asn Val Ser Leu Gln Asp Ser Gly Thr Tyr Ala Cys Arg Ala Arg Asn
625                 630                 635                 640

Val Tyr Thr Gly Glu Glu Ile Leu Gln Lys Lys Glu Ile Thr Ile Arg
                645                 650                 655

Asp Gln Glu Ala Pro Tyr Leu Leu Arg Asn Leu Ser Asp His Thr Val
            660                 665                 670

Ala Ile Ser Ser Ser Thr Thr Leu Asp Cys His Ala Asn Gly Val Pro
        675                 680                 685

Glu Pro Gln Ile Thr Trp Phe Lys Asn Asn His Lys Ile Gln Gln Glu
    690                 695                 700

Pro Gly Ile Ile Leu Gly Pro Gly Ser Ser Thr Leu Phe Ile Glu Arg
705                 710                 715                 720

Val Thr Glu Glu Asp Glu Gly Val Tyr His Cys Lys Ala Thr Asn Gln
                725                 730                 735

Lys Gly Ser Val Glu Ser Ser Ala Tyr Leu Thr Val Gln Gly Thr Ser
            740                 745                 750

Asp Lys Ser Asn Leu Glu Leu Ile Thr Leu Thr Cys Thr Cys Val Ala
        755                 760                 765

Ala Thr Leu Phe Trp Leu Leu Leu Thr Leu Phe Ile Arg Lys Met Lys
    770                 775                 780

Arg Ser Ser Ser Glu Ile Lys Thr Asp Tyr Leu Ser Ile Ile Met Asp
785                 790                 795                 800

Pro Asp Glu Val Pro Leu Asp Glu Gln Cys Glu Arg Leu Pro Tyr Asp
                805                 810                 815

Ala Ser Lys Trp Glu Phe Ala Arg Glu Arg Leu Lys Leu Gly Lys Ser
            820                 825                 830

Leu Gly Arg Gly Ala Phe Gly Lys Val Val Gln Ala Ser Ala Phe Gly
        835                 840                 845

Ile Lys Lys Ser Pro Thr Cys Arg Thr Val Ala Val Lys Met Leu Lys
    850                 855                 860

Glu Gly Ala Thr Ala Ser Glu Tyr Lys Ala Leu Met Thr Glu Leu Lys
865                 870                 875                 880

Ile Leu Thr His Ile Gly His His Leu Asn Val Val Asn Leu Leu Gly
                885                 890                 895

Ala Cys Thr Lys Gln Gly Gly Pro Leu Met Val Ile Val Glu Tyr Cys
            900                 905                 910

Lys Tyr Gly Asn Leu Ser Asn Tyr Leu Lys Ser Lys Arg Asp Leu Phe
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        915                 920                 925

Phe Leu Asn Lys Asp Ala Ala Leu His Met Glu Pro Lys Lys Glu Lys
    930                 935                 940

Met Glu Pro Gly Leu Glu Gln Gly Lys Lys Pro Arg Leu Asp Ser Val
945                 950                 955                 960

Thr Ser Ser Glu Ser Phe Ala Ser Ser Gly Phe Gln Glu Asp Lys Ser
                965                 970                 975

Leu Ser Asp Val Glu Glu Glu Glu Asp Ser Asp Gly Phe Tyr Lys Glu
            980                 985                 990

Pro Ile Thr Met Glu Asp Leu Ile  Ser Tyr Ser Phe Gln  Val Ala Arg
        995                 1000                1005

Gly Met  Glu Phe Leu Ser Ser  Arg Lys Cys Ile His  Arg Asp Leu
    1010                1015                1020

Ala Ala  Arg Asn Ile Leu Leu  Ser Glu Asn Asn Val  Val Lys Ile
    1025                1030                1035

Cys Asp  Phe Gly Leu Ala Arg  Asp Ile Tyr Lys Asn  Pro Asp Tyr
    1040                1045                1050

Val Arg  Lys Gly Asp Thr Arg  Leu Pro Leu Lys Trp  Met Ala Pro
    1055                1060                1065

Glu Ser  Ile Phe Asp Lys Ile  Tyr Ser Thr Lys Ser  Asp Val Trp
    1070                1075                1080

Ser Tyr  Gly Val Leu Leu Trp  Glu Ile Phe Ser Leu  Gly Gly Ser
    1085                1090                1095

Pro Tyr  Pro Gly Val Gln Met  Asp Glu Asp Phe Cys  Ser Arg Leu
    1100                1105                1110

Arg Glu  Gly Met Arg Met Arg  Ala Pro Glu Tyr Ser  Thr Pro Glu
    1115                1120                1125

Ile Tyr  Gln Ile Met Leu Asp  Cys Trp His Arg Asp  Pro Lys Glu
    1130                1135                1140

Arg Pro  Arg Phe Ala Glu Leu  Val Glu Lys Leu Gly  Asp Leu Leu
    1145                1150                1155

Gln Ala  Asn Val Gln Gln Asp  Gly Lys Asp Tyr Ile  Pro Ile Asn
    1160                1165                1170

Ala Ile  Leu Thr Gly Asn Ser  Gly Phe Thr Tyr Ser  Thr Pro Ala
    1175                1180                1185

Phe Ser  Glu Asp Phe Phe Lys  Glu Ser Ile Ser Ala  Pro Lys Phe
    1190                1195                1200

Asn Ser  Gly Ser Ser Asp Asp  Val Arg Tyr Val Asn  Ala Phe Lys
    1205                1210                1215

Phe Met  Ser Leu Glu Arg Ile  Lys Thr Phe Glu Glu  Leu Leu Pro
    1220                1225                1230

Asn Ala  Thr Ser Met Phe Asp  Asp Tyr Gln Gly Asp  Ser Ser Thr
    1235                1240                1245

Leu Leu  Ala Ser Pro Met Leu  Lys Arg Phe Thr Trp  Thr Asp Ser
    1250                1255                1260

Lys Pro  Lys Ala Ser Leu Lys  Ile Asp Leu Arg Val  Thr Ser Lys
    1265                1270                1275

Ser Lys  Glu Ser Gly Leu Ser  Asp Val Ser Arg Pro  Ser Phe Cys
    1280                1285                1290

His Ser  Ser Cys Gly His Val  Ser Glu Gly Lys Arg  Arg Phe Thr
    1295                1300                1305
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Tyr Asp  His Ala Glu Leu Glu  Arg Lys Ile Ala Cys  Cys Ser Pro
    1310                1315                1320

Pro Pro  Asp Tyr Asn Ser Val  Val Leu Tyr Ser Thr  Pro Pro Ile
    1325                1330                1335


<210> SEQ ID NO 11
<211> LENGTH: 296
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<223> OTHER INFORMATION: an amino acid sequence of sFlt-1 Ig-like
      domains 1, 2 and 3

<400> SEQUENCE: 11

Pro Glu Leu Ser Leu Lys Gly Thr Gln His Ile Met Gln Ala Gly Gln
1               5                   10                  15

Thr Leu His Leu Gln Cys Arg Gly Glu Ala Ala His Lys Trp Ser Leu
            20                  25                  30

Pro Glu Met Val Ser Lys Glu Ser Glu Arg Leu Ser Ile Thr Lys Ser
        35                  40                  45

Ala Cys Gly Arg Asn Gly Lys Gln Phe Cys Ser Thr Leu Thr Leu Asn
    50                  55                  60

Thr Ala Gln Ala Asn His Thr Gly Phe Tyr Ser Cys Lys Tyr Leu Ala
65                  70                  75                  80

Val Pro Thr Ser Lys Lys Lys Glu Thr Glu Ser Ala Ile Tyr Ile Phe
                85                  90                  95

Ile Ser Asp Thr Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro
            100                 105                 110

Glu Ile Ile His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg
        115                 120                 125

Val Thr Ser Pro Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp
    130                 135                 140

Thr Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly
145                 150                 155                 160

Phe Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys
                165                 170                 175

Glu Ala Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His
            180                 185                 190

Arg Gln Thr Asn Thr Ile Ile Asp Val Gln Ile Ser Thr Pro Arg Pro
        195                 200                 205

Val Lys Leu Leu Arg Gly His Thr Leu Val Leu Asn Cys Thr Ala Thr
    210                 215                 220

Thr Pro Leu Asn Thr Arg Val Gln Met Thr Trp Ser Tyr Pro Asp Glu
225                 230                 235                 240

Lys Asn Lys Arg Ala Ser Val Arg Arg Arg Ile Asp Gln Ser Asn Ser
                245                 250                 255

His Ala Asn Ile Phe Tyr Ser Val Leu Thr Ile Asp Lys Met Gln Asn
            260                 265                 270

Lys Asp Lys Gly Leu Tyr Thr Cys Arg Val Arg Ser Gly Pro Ser Phe
        275                 280                 285

Lys Ser Val Asn Thr Ser Val His
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290 295

<210> SEQ ID NO 12
<211> LENGTH: 177
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<223> OTHER INFORMATION: an amino acid sequence of sFlt-1 Ig-like domains 2 and 3

<400> SEQUENCE: 12

Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
1 5 10 15

Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys
20 25 30

Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
35 40 45

Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
50 55 60

Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
65 70 75 80

Asp Val Gln Ile Ser Thr Pro Arg Pro Val Lys Leu Leu Arg Gly His
85 90 95

Thr Leu Val Leu Asn Cys Thr Ala Thr Thr Pro Leu Asn Thr Arg Val
100 105 110

Gln Met Thr Trp Ser Tyr Pro Asp Glu Lys Asn Lys Arg Ala Ser Val
115 120 125

Arg Arg Arg Ile Asp Gln Ser Asn Ser His Ala Asn Ile Phe Tyr Ser
130 135 140

Val Leu Thr Ile Asp Lys Met Gln Asn Lys Asp Lys Gly Leu Tyr Thr
145 150 155 160

Cys Arg Val Arg Ser Gly Pro Ser Phe Lys Ser Val Asn Thr Ser Val
165 170 175

His

<210> SEQ ID NO 13
<211> LENGTH: 398
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<223> OTHER INFORMATION: an amino acid sequence of PEDF

<400> SEQUENCE: 13

Asn Pro Ala Ser Pro Pro Glu Glu Gly Ser Pro Asp Pro Asp Ser Thr
1 5 10 15

Gly Ala Leu Val Glu Glu Glu Asp Pro Phe Phe Lys Val Pro Val Asn
20 25 30

Lys Leu Ala Ala Ala Val Ser Asn Phe Gly Tyr Asp Leu Tyr Arg Val
35 40 45

Arg Ser Ser Met Ser Pro Thr Thr Asn Val Leu Leu Ser Pro Leu Ser
50 55 60

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Val Ala Thr Ala Leu Ser Ala Leu Ser Leu Gly Ala Asp Glu Arg Thr
65                  70                  75                  80

Glu Ser Ile Ile His Arg Ala Leu Tyr Tyr Asp Leu Ile Ser Ser Pro
                85                  90                  95

Asp Ile His Gly Thr Tyr Lys Glu Leu Leu Asp Thr Val Thr Ala Pro
            100                 105                 110

Gln Lys Asn Leu Lys Ser Ala Ser Arg Ile Val Phe Glu Lys Lys Leu
        115                 120                 125

Arg Ile Lys Ser Ser Phe Val Ala Pro Leu Glu Lys Ser Tyr Gly Thr
    130                 135                 140

Arg Pro Arg Val Leu Thr Gly Asn Pro Arg Leu Asp Leu Gln Glu Ile
145                 150                 155                 160

Asn Asn Trp Val Gln Ala Gln Met Lys Gly Lys Leu Ala Arg Ser Thr
                165                 170                 175

Lys Glu Ile Pro Asp Glu Ile Ser Ile Leu Leu Leu Gly Val Ala His
            180                 185                 190

Phe Lys Gly Gln Trp Val Thr Lys Phe Asp Ser Arg Lys Thr Ser Leu
        195                 200                 205

Glu Asp Phe Tyr Leu Asp Glu Glu Arg Thr Val Arg Val Pro Met Met
    210                 215                 220

Ser Asp Pro Lys Ala Val Leu Arg Tyr Gly Leu Asp Ser Asp Leu Ser
225                 230                 235                 240

Cys Lys Ile Ala Gln Leu Pro Leu Thr Gly Ser Met Ser Ile Ile Phe
                245                 250                 255

Phe Leu Pro Leu Lys Val Thr Gln Asn Leu Thr Leu Ile Glu Glu Ser
            260                 265                 270

Leu Thr Ser Glu Phe Ile His Asp Ile Asp Arg Glu Leu Lys Thr Val
        275                 280                 285

Gln Ala Val Leu Thr Val Pro Lys Leu Lys Leu Ser Tyr Glu Gly Glu
    290                 295                 300

Val Thr Lys Ser Leu Gln Glu Met Lys Leu Gln Ser Leu Phe Asp Ser
305                 310                 315                 320

Pro Asp Phe Ser Lys Ile Thr Gly Lys Pro Ile Lys Leu Thr Gln Val
                325                 330                 335

Glu His Arg Ala Gly Phe Glu Trp Asn Glu Asp Gly Ala Gly Thr Thr
            340                 345                 350

Pro Ser Pro Gly Leu Gln Pro Ala His Leu Thr Phe Pro Leu Asp Tyr
        355                 360                 365

His Leu Asn Gln Pro Phe Ile Phe Val Leu Arg Asp Thr Asp Thr Gly
    370                 375                 380

Ala Leu Leu Phe Ile Gly Lys Ile Leu Asp Pro Arg Gly Pro
385                 390                 395


<210> SEQ ID NO 14
<211> LENGTH: 27
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<223> OTHER INFORMATION: an amino acid sequence of BLP-1 peptide

<400> SEQUENCE: 14
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Gly Ile Gly Ala Ser Ile Leu Ser Ala Gly Lys Ser Ala Leu Lys Gly
1               5                   10                  15

Leu Ala Lys Gly Leu Ala Glu His Phe Ala Asn
            20                  25


<210> SEQ ID NO 15
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<223> OTHER INFORMATION: an amino acid sequence of parasin-1 peptide

<400> SEQUENCE: 15

Lys Gly Arg Gly Lys Gln Gly Gly Lys Val Arg Ala Lys Ala Lys Thr
1               5                   10                  15

Arg Ser Ser


<210> SEQ ID NO 16
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<223> OTHER INFORMATION: an amino acid sequence of magainin-2 peptide

<400> SEQUENCE: 16

Gly Ile Gly Lys Phe Leu His Ser Ala Gly Lys Phe Gly Lys Ala Phe
1               5                   10                  15

Val Gly Glu Ile Met Lys Ser
            20


<210> SEQ ID NO 17
<211> LENGTH: 24
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<223> OTHER INFORMATION: an amino acid sequence of a ranalexin peptide

<400> SEQUENCE: 17

Phe Phe Gly Gly Leu Ile Lys Ile Val Pro Ala Met Ile Pro Lys Ile
1               5                   10                  15

Phe Cys Lys Ile Thr Arg Lys Cys
            20
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1. A method of delivering a therapeutic agent to an eye, comprising: administering to the eye of a subject an effective amount of a compound that comprises an elastin-like polypeptide (ELP) coupled to a therapeutic agent, wherein the ELP comprises at least one repeat of the amino acid sequence VPGXG (SEQ ID NO: 1).

2. The method of claim **1**, wherein administration comprises one or more of topical administration, subconjunctival administration, and intraocular injection.

3. The method of claim **1**, wherein a size of the ELP is configured to permit ocular penetration of the compound.

4. The method of claim **3**, wherein the ELP comprises about 5 to about 300 VPGXG sequences.

5. (canceled)

6. (canceled)

7. (canceled)

8. The method of claim **1**, wherein the X amino acid is hydrophilic to permit stability of the compound in the ocular environment.

9. The method of claim **8**, wherein X is selected from a mixture of Val, Ala, and Gly in a 1:8:7 ratio (SEQ ID NO:2),

a mixture of Val, Ala, and Gly in a 1:4:3 ratio (SEQ ID NO:3), Gly (SEQ ID NO: 4), Ser (SEQ ID NO: 5), or His (SEQ ID NO:6).

10. (canceled)

11. (canceled)

12. (canceled)

13. (canceled)

14. The method of claim **1**, wherein X is hydrophobic to permit corneal penetration of the compound.

15. The method of claim **14**, wherein X is selected from Val (SEQ ID NO:7), Leu (SEQ ID NO: 8), or Ile (SEQ ID NO:9).

16. (canceled)

17. (canceled)

18. The method of claim **1**, wherein the compound further comprises a cell-penetrating peptide (CPP) coupled to the ELP.

19. The method of claim **18**, wherein the cell-penetrating peptide is selected from penetratin, Tat, SynB1, Bac, polyArg, MTS, Transportan, and pVEC.

20. The method of claim **1**, wherein the compound further comprises an attachment site configured to couple to a therapeutic agent.

21. The method of claim **20**, wherein the attachment site comprises one or more Cys or Lys residues at a N-terminus, a C-terminus, or an interior of the compound.

22. (canceled)

23. The method of claim **1**, wherein the compound forms a hydrogel after topical application or intraocular injection.

24. The method of claim **23**, wherein the compound has a phase transition below the ocular temperature, and wherein ocular injection or application induces phase transfer and hydrogel formation.

25. The method of claim **23**, wherein the hydrogel formation increases ocular residence time and bioavailability of the therapeutic.

26. The method of claim **1**, wherein the therapeutic agent is linked to the ELP carrier with a cleavable linker to allow release of the therapeutic agent intraocularly.

27. The method of claim **1**, wherein the administering of the compound further comprises treating a disorder in the subject.

28. The method of claim **27**, wherein the therapeutic agent is a VEGF antagonist.

29. The method of claim **27**, wherein the therapeutic agent is a member of the sFlt-1 family, a portion of the sFlt-1 protein (SEQ ID NO:10), or a combination thereof.

30. The method of claim **27**, herein the therapeutic agent is sFlt-1 Ig-like domains 1, 2, and 3 (SEQ ID NO:11).

31. The method of claim **27**, wherein the therapeutic agent is sFlt-1 Ig-like domains 2 and 3 (SEQ ID NO:12).

32. The method of claim **27**, wherein the therapeutic agent is PEDF (SEQ ID NO:13).

33. The method of claim **28**, wherein the therapeutic agent is an anti-inflammatory drug, an anti-inflammatory peptide, or a combination thereof.

34. The method of claim **27**, further comprising a cell-penetrating peptide.

35. The method of claim **34**, wherein the cell penetrating peptide is selected from penetratin, Tat, SynB1, Bac, polyArg, MTS, Transportan, POD, and pVEC.

36. The method of claim **27**, wherein the disorder is selected from the group consisting of an ocular infection and a neovascularization disorder.

37. (canceled)

38. (canceled)

39. (canceled)

40. (canceled)

41. (canceled)

42. (canceled)

43. A composition, comprising:

a compound that comprises an elastin-like polypeptide (ELP) coupled to a therapeutic agent, wherein the ELP comprises at least one repeat of the amino acid sequence VPGXG (SEQ ID NO: 1).

44. The composition of claim **43**, wherein the composition is eye drops, an ointment, or a combination thereof.

45. The composition of claim **43**, further comprising at least one thickening agent selected from a group consisting of polyvinyl alcohol, polyethylene glycol, methyl cellulose, and carboxymethyl cellulose.

46. The composition of claim **43**, further comprising an agent modulating tonicity, wherein the agent is boric acid or sodium phosphate buffer.

47. The composition of claim **43**, further comprising at least one surfactant to increase corneal penetration, wherein the at least one surfactant is selected from a group consisting of benzalkonium chloride, polysorbate 20, polysorbate 80, and dioctyl sodium sulpho succinate.

48. The composition of claim **43**, further comprising a buffering agent to adjust the pH of the solution.

49. The composition of claim **43**, wherein the ELP comprises about 5 to about 300 VPGXG sequences.

50. The composition of claim **43**, wherein the X amino acid is hydrophilic, hydrophobic, or a combination thereof.

51. The composition of claim **43**, wherein X is at least one selecting from Val, Ala, or Gly in a 1:8:7 ratio (SEQ ID NO:2), Val, Ala, or Gly in a 1:4:3 ratio (SEQ ID NO:3), Gly (SEQ ID NO:4), Ser (SEQ ID NO:5), His (SEQ ID NO:6), Val (SEQ ID NO:7), Leu (SEQ ID NO:8), Ile (SEQ ID NO:9), and a combination thereof.

52. The composition of claim **43**, wherein the compound further comprises a cell-penetrating peptide (CPP) coupled to the ELP.

53. The composition of claim **52**, herein the cell-penetrating peptide is selected from penetratin, Tat, SynB1, Bac, polyArg, MTS, Transportan, POD, and pVEC.

54. The composition of claim **43**, wherein the compound further comprises an attachment site configured to couple to a therapeutic agent.

55. The composition of claim **54**, wherein the attachment site comprises one or more Cys residues, one or more Lys residues, or a combination thereof.

56. The composition of claim **43**, wherein the therapeutic agent is at least one selected from a group consisting of a VEGF antagonist, a member of the sFlt-1 family, a portion of the sFlt-1 protein (SEQ ID NO:10), sFlt-1 Ig-like domains 1, 2, 3 (SEQ ID NO:11), PEDF (SEQ ID NO:13), an anti-inflammatory drug and/or peptide, a BLP-1 peptide (SEQ ID NO:14), a parasin-1 peptide (SEQ ID NO:15), a magainin-2 peptide (SEQ ID NO:16), and a ranalexin peptide (SEQ ID NO:17).

57. The composition of claim **43**, wherein the ELP comprises at least about 5 repeats of the amino acid sequence VPGXG (SEQ ID NO: 1).

58. (canceled)

59. (canceled)

60. (canceled)

61. (canceled)
62. (canceled)
63. (canceled)
64. (canceled)
65. (canceled)
66. The composition of claim **43**, further comprising a pharmaceutically acceptable carrier for topical delivery to an eye.

* * * * *