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(54) Title: TREATMENT OF CORNEAL HAZE

Figure 3.

(57) Abstract: There are provided methods and pharmaceutical compositions for prevention and/or treatment of ocular fibrosis of the cornea, lens and/or lens capsule.
TREATMENT OF CORNEAL HAZE

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] NOT APPLICABLE

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] NOT APPLICABLE

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK

[0003] NOT APPLICABLE

BACKGROUND OF THE INVENTION

[0004] Corneal injury, surgery or infection often results in loss of stromal transparency (Wilson, 2012). Corneal myofibroblast generation associated with a decrease in expression of corneal crystallins by these cells and production of abnormal extracellular matrix have been identified as important biological events that lead to corneal opacity (clinically referred to as haze) during corneal wound healing (Jester et al., 1999; Mohan et al., 2003; Netto et al., 2006).

[0005] Myofibroblasts are fibroblastic cells that are generated from both keratocyte-derived and bone marrow-derived precursor cells (Barbosa et al., 2010a; Novo et al., 2009; Saika, 2006). Epithelial-stromal interactions modulate the generation of corneal myofibroblasts and the development of stromal opacity (Wilson et al., 1999). Myofibroblast development and persistence appear to occur when structural and functional defects in the regenerated epithelial basement membrane facilitate the penetration of transforming growth factor beta (TGF-β) and platelet-derived growth factor (PDGF) from the epithelium into the anterior stroma at sufficient levels required for ongoing receptor activation in precursor cells (Kaur et al., 2009; Netto et al., 2006; Torricelli et al., 2013). TGF-β promotes myofibroblast development (Chaurasia et al., 2009) and suppresses interleukin-1 (IL-1)-mediated apoptosis of myofibroblasts and their precursors (Barbosa et al., 2010b; Kaur et al., 2009).
Resolvins belong to a novel class of lipid-derived endogenous molecules that have potent immunomodulatory properties and have been shown to regulate the resolution phase of an active immune response (Levy, 2010; Serhan et al., 2008). These modulators are derived from omega-3 polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and can be categorized in E-series (from EPA) or D-series (from DHA) (Levy, 2010; Serhan and Chiang, 2008). Resolvin E1 (RvEl: 5S,12R,18R-trihydroxy eicosapentaenoic acid) was the first resolvin described in inflammatory exudates of acute inflammation in mice (Serhan et al., 2000). Some of the RvEl effects are related to reduction of polymorphonuclear neutrophil infiltration (Serhan et al., 2008), increased macrophage phagocytosis of apoptotic neutrophils, and inhibition of the host tissue inflammatory response (Bannenberg and Serhan, 2010). Resolvins have been shown to be effective in a range of experimental models of inflammatory diseases, including pneumonitis (Haworth et al., 2008), colitis (Ishida et al., 2010), and periodontitis (Hasturk et al., 2007), as well as eye disorders such as retinal angiogenesis (Connor et al., 2007), dry eye (Li et al., 2010), and herpes simplex virus-induced ocular inflammation (Rajasagi et al., 2011). In addition, RvEl was investigated in human corneal epithelial cell wound model in vitro and was found to promote wound closure and to reduce cytokine and chemokine release (Zhang et al., 2010).

**SUMMARY OF THE INVENTION**

To fill an unmet need, there are provided herein methods and pharmaceutical compositions.

In a first aspect, there is provided a method for the prevention and/or treatment of ocular fibrosis of the cornea, lens and/or lens capsule. The method includes administering to a subject in need thereof an effective amount of an active agent as disclosed herein. The term "active agent" and the like refer, in the usual and customary sense, to any agent capable of affecting a biological process, e.g., a compound with structure of any one of Formula (I) or (Fa)-(I'h). In aspects and embodiments the active agent is a compound of formula A, a compound of any one of formulae 1-49, a compound of any one of formulae I-III, a lipoxin compound, an oxylipin compound, a prodrug of any of the foregoing, or a pharmaceutically acceptable salt of any of the foregoing, as set forth in Int. Appl. No. PCT/US2009/058016, filed September 23, 2009, incorporated herein by reference in its entirety and for all purposes.
In some embodiments, the active agent is a compound with structure of formula A, a compound of any one of formulae 1-46, a lipoxin compound, or an oxylipin compound as set forth in Int. Appl. No. PCT/PCT/US2007/016338, filed July 19, 2007, incorporated herein by reference in its entirety and for all purposes.

In some embodiments, the active agent is a compound of formula A, a compound of any one of formulae 1-49, a lipoxin compound, an oxylipin compound, a prodrug of any of the foregoing, or a pharmaceutically acceptable salt of any of the foregoing, as set forth in Int. Appl. No. PCT/US2008/01664, filed October 10, 2008, incorporated herein by reference in its entirety and for all purposes.

In some embodiments, the active agent is a compound with structure of Formula (F) where \( R \) is hydrogen or substituted or unsubstituted alkyl.

In some embodiments, the active agent is a compound with structure of Formula (Fa):

\[
(I'),
\]

wherein \( R \) is hydrogen or substituted or unsubstituted alkyl.

In some embodiments, the active agent is a compound with structure of Formula (Fb):

\[
(I'a),
\]

wherein \( R \) is hydrogen or substituted or unsubstituted alkyl.

In some embodiments, the active agent is a compound with structure of Formula (Fb):

\[
(I'b),
\]
wherein R is hydrogen or substituted or unsubstituted alkyl.

[0014] In some embodiments, the active agent is a compound with structure of Formula (I’c):

![Structure (I’c)]

wherein R is hydrogen or substituted or unsubstituted alkyl.

[0015] In some embodiments, the active agent is a compound with structure of Formula (I’d):

![Structure (I’d)]

wherein R is hydrogen or substituted or unsubstituted alkyl.

[0016] In some embodiments, the active agent is a compound with structure of Formula (I’e):

![Structure (I’e)]

wherein R is hydrogen or substituted or unsubstituted alkyl.

[0017] In some embodiments, the active agent is a compound with structure of Formula (I’f):

![Structure (I’f)]
wherein R is hydrogen or substituted or unsubstituted alkyl.

[0018] In some embodiments, the active agent is a compound with structure of Formula (I'g):

\[
\text{OH} \quad \text{OH} \quad \text{O} \quad \text{R}
\]

\[
(\text{I'}\text{g}),
\]

wherein R is hydrogen or substituted or unsubstituted alkyl.

[0019] In some embodiments, the active agent is a compound with structure of Formula (I'h):

\[
\text{OH} \quad \text{OH} \quad \text{O} \quad \text{R}
\]

\[
(\text{I'}\text{h}),
\]

wherein R is hydrogen or substituted or unsubstituted alkyl.

[0020] In some embodiments, the method includes administering to a subject in need thereof an effective amount of the compound with structure of any one of Formulae (Γ) or (Γ'a)-(Γ'h), wherein R is hydrogen or Ci-C₆ alkyl.

[0021] In some embodiments, the method includes administering to a subject in need thereof an effective amount of the compound with structure of Formula (Fa), wherein R is hydrogen or Ci-C₆ alkyl. In some embodiments, the method includes administering to a subject in need thereof an effective amount of the compound with structure of Formula (I'b), wherein R is hydrogen or Ci-C₆ alkyl. In some embodiments, the method includes administering to a subject in need thereof an effective amount of the compound with structure of Formula (I'c), wherein R is hydrogen or Ci-C₆ alkyl. In some embodiments, the method includes administering to a subject in need thereof an effective amount of the compound with structure of Formula (I'd), wherein R is hydrogen or Ci-C₆ alkyl. In some embodiments, the method includes administering
to a subject in need thereof an effective amount of the compound with structure of Formula (I'e),
wherein R is hydrogen or C1-C6 alkyl. In some embodiments, the method includes administering
to a subject in need thereof an effective amount of the compound with structure of Formula (I'f),
wherein R is hydrogen or C1-C6 alkyl. In some embodiments, the method includes administering
to a subject in need thereof an effective amount of the compound with structure of Formula (I'g),
wherein R is hydrogen or C1-C6 alkyl. In some embodiments, the method includes administering
to a subject in need thereof an effective amount of the compound with structure of Formula (I'h),
wherein R is hydrogen or C1-C6 alkyl.

[0022] In some embodiments, R is alkyl optionally substituted independently with halogen,
-CN, -CF3, -OH, -NH2, -S02, substituted or unsubstituted alkyl, substituted or unsubstituted
heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
hetereocyloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In
some embodiments, R is size-limited substituted alkyl. In some embodiments, R is C1-C2, C1-C3,
C1-C4, C1-C5, or C1-C6 substituted alkyl. In some embodiments, R is C1-C5 alkyl, C1-C6 alkyl, C1-C7 alkyl or C1-C8 alkyl. In some embodiments, R is C1-C6 alkyl. In
some embodiments, R is methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl,
hexyl, or isomer thereof. Further to any embodiment set forth herein, in some embodiments R is
hydrogen. Further to any embodiment set forth herein, in some embodiments R is isopropyl.

[0023] In some embodiments, the above-described method is useful to prevent ocular fibrosis
of the cornea, lens and/or lens capsule. The term "corneal fibrosis" is used synonymously herein
in reference to ocular fibrosis of the cornea, lens or lens capsule. In some embodiments, the
method is useful to treat ocular fibrosis of the cornea, lens and lens capsule. The term "ocular
fibrosis" and the like refer, in the usual and customary sense, to a response of the eye to injury.
The injury can occur as a result of a mechanical wound (e.g., surgery, trauma and the like) or
other conditions including responses to inflammation, ischemia, and degenerative disease. The
local response of the eye involved with ocular fibrosis can include infiltration by inflammatory
cells, neovascularization, altered vascular permeability, proliferation of fibroblasts and
fibroblast-like cells, and modification of the extracellular matrix involved in wound-healing and scar-formation events. The terms "crystalline lens," "natural lens," "lens" and the like refer, in the usual and customary sense, to the transparent and biconvex physiologic structure of the eye which lies within the anterior segment of the eye, proximal to the cornea, through which light passes in transit to the retina. As known in the art, the lens includes three distinct parts: the lens capsule, the lens epithelium and the lens fibers. The term "lens capsule" and the like refer, in the usual and customary sense, to the smooth and transparent basement membrane that encompasses the lens. The term "lens epithelium" and the like refer, in the usual and customary sense, to the epithelial layer located at the anterior portions of the lens between the lens capsule and the lens fibers. The term "lens fiber" and the like refer, in the usual and customary sense, to the long, thin and transparent cells forming the bulk of the lens.

[0025] In some embodiments, the ocular fibrosis results from inflammatory cells or by proliferation of fibroblasts or fibroblast-like cells activated as a result of trauma, infection or surgery. In some embodiments, the ocular fibrosis results from inflammatory cells activated as a result of trauma, infection or surgery. In some embodiments, the ocular fibrosis results from inflammatory cells activated as a result of trauma. In some embodiments, the ocular fibrosis results from inflammatory cells activated as a result of infection. In some embodiments, the ocular fibrosis results from inflammatory cells activated as a result of surgery. In some embodiments, the ocular fibrosis results from proliferation of fibroblasts or fibroblast-like cells activated as a result of trauma, infection or surgery. In some embodiments, the ocular fibrosis results from proliferation of fibroblasts activated as a result of trauma, infection or surgery. In some embodiments, the ocular fibrosis results from proliferation of fibroblasts activated as a result of trauma. In some embodiments, the ocular fibrosis results from proliferation of fibroblasts activated as a result of infection. In some embodiments, the ocular fibrosis results from proliferation of fibroblasts activated as a result of surgery. In some embodiments, the ocular fibrosis results from proliferation of fibroblasts activated as a result of surgery. In some embodiments, the ocular fibrosis results from proliferation of fibroblast-like cells activated as a result of trauma, infection or surgery. In some embodiments, the ocular fibrosis results from proliferation of fibroblast-like cells activated as a result of trauma. In some embodiments, the ocular fibrosis results from proliferation of fibroblast-like cells activated as a result of infection. In some embodiments, the ocular fibrosis results from proliferation of fibroblast-like cells activated as a result of surgery. The term "fibroblast" and the like refer, in the usual and customary sense, to
cells, typically of connective tissue, which synthesize the extracellular matrix, collagen, and/or stroma, as well known in the art. The terms "fibroblast-like cell," "FLC," and the like refer, in the usual and customary sense, to cells closely related to fibroblasts yet having morphological differences, as known in the art.

[0026] In some embodiments, the surgery is laser-assisted in situ keratomileusis (LASIK), laser-assisted epithelial keratoplasty (LASEK) or photorefractive keratectomy (PRK). In some embodiments, the surgery is LASIK. In some embodiments, the surgery is LASEK. In some embodiments, the surgery is PRK.

[0027] In some embodiments, the surgery involves removal of the natural lens and the implantation of an artificial intraocular lens. The term "intraocular lens" and the like refer, in the usual and customary sense, to a lens implanted in the eye to replace a diseased or otherwise injured lens.

[0028] In some embodiments, the surgery is corneal transplantation. In some embodiments, the corneal transplantation procedure includes penetrating keratoplasty, lamellar keratoplasty, anterior lamellar keratoplasty, deep anterior lamellar keratoplasty or endothelial keratoplasty. In some embodiments, the corneal transplantation procedure includes penetrating keratoplasty, wherein a damaged or diseased cornea is replaced in its entirety with donated corneal tissue. In some embodiments, the corneal transplantation procedures includes lamellar keratoplasty, wherein a damaged or diseased cornea is replaced in part with donated corneal tissue. In some embodiments, the corneal transplantation procedures includes anterior lamellar keratoplasty, wherein the anterior portion of a damaged or diseased cornea is excised and replaced with matching donor tissue. In some embodiments, the corneal transplantation procedures includes deep anterior lamellar keratoplasty, wherein a portion of a damaged or diseased cornea including the corneal stroma down to Descemet's membrane is excised and replaced with matching donor tissue. In some embodiments, the corneal transplantation procedures includes endothelial keratoplasty, wherein the endothelium of a damaged or diseased cornea is excised and replaced with matching donor tissue.

[0029] In some embodiments, the surgery is pterygium excision. As known in the art, pterygium (pi. pterygia) refers to a growth of tissue (e.g., a non-cancerous growth) that forms on the conjunctiva. A pterygium may present as a fleshy mass that is felt and/or seen at the
conjunctiva, and larger growths may extend across the cornea. Thus, pterygium excision refers to surgical removal of a pterygium.

[0030] In some embodiments, the ocular fibrosis results from inflammatory cells or by proliferation of fibroblasts or fibroblast-like cells activated as a result of infection, wherein the infection gives rise to bacterial or viral keratitis. The term "bacterial keratitis" and the like refer, in the usual and customary sense, to a bacterial infection of the cornea, typically accompanied by pain, reduced vision, light sensitivity, and tearing or dispatch from the eye. The term "viral keratitis" and the like refer, in the usual and customary sense, to a viral infection of the eye (e.g., the cornea). Causative viral infections associate with viral keratitis include Adenovirus, Herpes simplex type 1, and Varicella zoster.

[0031] In some embodiments, the ocular fibrosis is stromal haze. The term "corneal haze" and the like refer, in the usual and customary sense, to a cornea which has become cloudy or opaque with attending vision impairment. Corneal haze can occur in any part of the cornea, and when observed in the stroma it is referred to as "stromal haze."

[0032] In some embodiments, the ocular fibrosis is pterygia, as known in the art.

[0033] In some embodiments, the ocular fibrosis is of the lens capsule. In some embodiments, the ocular fibrosis of the lens capsule is posterior capsule opacification (PCO) incident to cataract surgery. As known in the art, the term "posterior capsule opacification," "PCO" and the like refer to a hazy membrane that can form adjacent to an intraocular lens implant. Without wishing to be bound by any theory, it is believed that in a small population (e.g., 10%) of subjects who have undergone cataract surgery, the outer cells of the old lens remain and grow on the lens capsule, resulting in the capsule becoming hazy or clouded, resulting in blurred vision.

[0034] In some embodiments, the cataract surgery is phacoemulsification, manual small incision cataract surgery, extracapsular cataract extraction, or intracapsular cataract extraction.
lens. In some embodiments, the cataract surgery is intracapsular cataract extraction, wherein the lens and surrounds lens capsule are removed in one piece.

[0035] In another aspect, there is provided a method for prevention and treatment of fibrotic invasion of the cornea, lens or lens capsule, the method including administering to a subject in need thereof an effective amount of an active agent as disclosed herein. In some embodiments, the active agent is a compound with structure of any one of Formulae (F) or (Fa)-(Fh). In some embodiments, the active agent is a compound with structure of Formula (F). In some embodiments, the active agent is a compound with structure of Formula (Fa). In some embodiments, the active agent is a compound with structure of Formula (Fb). In some embodiments, the active agent is a compound with structure of Formula (Fc). In some embodiments, the active agent is a compound with structure of Formula (I'd). In some embodiments, the active agent is a compound with structure of Formula (Fe). In some embodiments, the active agent is a compound with structure of Formula (Ff). In some embodiments, the active agent is a compound with structure of Formula (Fg). In some embodiments, the active agent is a compound with structure of Formula (Fh).

[0036] In some embodiments, the effective amount of the compound with structure of any one of Formulae (F) or (Fa)-(Fh) inhibits the production or transport of inflammatory cells to the cornea. In some embodiments, the effective amount of the compound with structure of Formula (F) inhibits the production or transport of inflammatory cells to the cornea. In some embodiments, the effective amount of the compound with structure of Formula (Fa) inhibits the production or transport of inflammatory cells to the cornea. In some embodiments, the effective amount of the compound with structure of Formula (Fb) inhibits the production or transport of inflammatory cells to the cornea. In some embodiments, the effective amount of the compound with structure of Formula (Fc) inhibits the production or transport of inflammatory cells to the cornea. In some embodiments, the effective amount of the compound with structure of Formula (I'd) inhibits the production or transport of inflammatory cells to the cornea. In some embodiments, the effective amount of the compound with structure of Formula (Fe) inhibits the production or transport of inflammatory cells to the cornea. In some embodiments, the effective amount of the compound with structure of Formula (Ff) inhibits the production or transport of inflammatory cells to the cornea. In some embodiments, the effective amount of the compound with structure of Formula (Fg) inhibits the production or transport of inflammatory cells to the cornea. In some embodiments, the effective amount of the compound with structure of Formula (Fh) inhibits the production or transport of inflammatory cells to the cornea.
with structure of Formula (Fg) inhibits the production or transport of inflammatory cells to the cornea. In some embodiments, the effective amount of the compound with structure of Formula (Fh) inhibits the production or transport of inflammatory cells to the cornea.

[0037] In some embodiments, the fibrotic invasion of the cornea, lens or lens capsule comprises myofibroblasts derived from bone marrow-derived fibrocysts or keratocyte-derived corneal fibroblasts.

[0038] In some embodiments, the effective amount of the compound with structure of any one of Formulae (F) or (Fa)-(Fh) is effective to block the transition of the myofibroblasts derived from bone marrow-derived fibrocysts or keratocyte-derived corneal fibroblasts in response to transforming growth factor beta (TGFP). In some embodiments, the effective amount of the compound with structure of Formula (F) is effective to block the transition of the myofibroblasts derived from bone marrow-derived fibrocysts or keratocyte-derived corneal fibroblasts in response to transforming growth factor beta (TGFP). In some embodiments, the effective amount of the compound with structure of Formula (Fa) is effective to block the transition of the myofibroblasts derived from bone marrow-derived fibrocysts or keratocyte-derived corneal fibroblasts in response to transforming growth factor beta (TGFP). In some embodiments, the effective amount of the compound with structure of Formula (Fb) is effective to block the transition of the myofibroblasts derived from bone marrow-derived fibrocysts or keratocyte-derived corneal fibroblasts in response to transforming growth factor beta (TGFP). In some embodiments, the effective amount of the compound with structure of Formula (Fc) is effective to block the transition of the myofibroblasts derived from bone marrow-derived fibrocysts or keratocyte-derived corneal fibroblasts in response to transforming growth factor beta (TGFP). In some embodiments, the effective amount of the compound with structure of Formula (Fd) is effective to block the transition of the myofibroblasts derived from bone marrow-derived fibrocysts or keratocyte-derived corneal fibroblasts in response to transforming growth factor beta (TGFP). In some embodiments, the effective amount of the compound with structure of Formula (Fe) is effective to block the transition of the myofibroblasts derived from bone marrow-derived fibrocysts or keratocyte-derived corneal fibroblasts in response to transforming growth factor beta (TGFP). In some embodiments, the effective amount of the compound with structure of Formula (Ff) is effective to block the transition of the myofibroblasts derived from
bone marrow-derived fibrocysts or keratocyte-derived corneal fibroblasts in response to transforming growth factor beta (TGFβ). In some embodiments, the effective amount of the compound with structure of Formula (I’g) is effective to block the transition of the myofibroblasts derived from bone marrow-derived fibrocysts or keratocyte-derived corneal fibroblasts in response to transforming growth factor beta (TGFβ).

[0039] In another aspect, there is provided a pharmaceutical composition for topical administration, including an active agent in combination with a pharmaceutically acceptable excipient, wherein the active agent is as disclosed herein.

[0040] In some embodiments, the pharmaceutical composition includes the compound with structure of Formula (Γ):

\[
\text{OH} \quad \text{OH} \quad \text{O} \quad \text{R}
\]

(Γ),

wherein R is hydrogen or substituted or unsubstituted alkyl, in combination with a pharmaceutically acceptable excipient. In some embodiments, R is hydrogen or C1-C6 alkyl.

[0041] In some embodiments, the pharmaceutical composition includes the compound with structure of any one of Formula (Fa)-(I’h), wherein R is hydrogen or substituted or unsubstituted alkyl, in combination with a pharmaceutically acceptable excipient. In some embodiments, R is hydrogen or C1-C6 alkyl.

[0042] In some embodiments, the pharmaceutical composition includes the compound with structure of Formula (I’h):
wherein R is hydrogen or substituted or unsubstituted alkyl, in combination with a pharmaceutically acceptable excipient. In some embodiments, R is hydrogen or Ci-C₆ alkyl.

[0043] In some embodiments, R is alkyl optionally substituted independently with halogen, -CN, -CF₃, -OH, -NH₂, -SO₂, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, R is size-limited substituted alkyl. In some embodiments, R is Ci-C₂, Ci-C₃, C₁-C₄, C₁-C₅, or Ci-C₆ substituted alkyl. In some embodiments, R is Ci, C₂, C₃, C₄, C₅, or C₆ substituted alkyl.

[0044] In some embodiments, R is unsubstituted alkyl. In some embodiments, R is size-limited unsubstituted alkyl. In some embodiments, R is Ci-C₂ alkyl, Ci-C₃ alkyl, C₁-C₄ alkyl, C₁-C₅ alkyl, or Ci-C₆ alkyl. In some embodiments, R is Ci-C₆ alkyl. In some embodiments, R is methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, hexyl, or isomer thereof. Further to any embodiment set forth herein, in some embodiments R is hydrogen. In some embodiments, R is isopropyl.

[0045] In some embodiments, the pharmaceutical composition as described herein may have certain surprising features and advantages that could not have been predicted prior to the present disclosure. For example, formulations of the instant disclosure may be able to support a dose of an active ingredient such as a hydrophobic active ingredient that is surprisingly higher than many prior art formulations. The dose of an active ingredient or agent used in the formulations described herein may be selected based on various criteria, including the amount that the formulation can support, the desired dose for various therapeutic applications, and the like. In this regard, in some embodiments the active ingredient (such as for ophthalmic administration) the active agent may be at least about 0.05%, or at least about 0.08%, or at least about 0.09%, or at least about 0.1%, or at least about 0.15%; or at least about 0.2%; or at least about 0.3%; or at
least about 0.4%; or at least about 0.5%; or at least about 0.6%; or at least about 0.7%; or at least about 0.8%; or at least about 0.9%; or at least about 1.0%; or at least about 1.5%; or at least about 2%; or at least about 3%; or at least about 4%; or at least about 5%; or between 0.05 and 5%; or between 0.05 and 0.5%; or between 0.05 and 0.2%, or between 0.08 and 0.12%; or between 0.1 and 0.5%, or between 0.5 and 1%, or between 0.5 and 1.5%; or between 1 and 5%; or between 2 and 4%; or between 4 and 6% of the formulation.

[0046] In some embodiments, there is provided a pharmaceutical composition that includes an active agent (e.g., a compound with structure of any one of Formulae (Γ) or (Γa)-(Γh)), a polyoxyl lipid or fatty acid and a polyalkoxylated alcohol. In some embodiments the polyoxyl lipid or fatty acid is a polyoxyl castor oil. In some embodiments, the polyoxyl lipid or fatty acid is one or more selected from HCO-40, HCO-60, HCO-80 or HCO-100. In some embodiments the polyoxyl lipid or fatty acid (such as a polyoxyl castor oil such as HCO-40, HCO-60, HCO-80 or HCO-100) is present between 1 and 6%; or 2 and 6%; or 2 and 6%; or 3 and 6%; or 4 and 6%; or 2 and 5%; or 3 and 5%; or 2 and 6%; or about 4%; or greater than 0.7%; or greater than 1%, or greater than 1.5%; or greater than 2%; or greater than 3%; or greater than 4% by weight of the formulation. In some embodiments the polyoxyl lipid is HCO-60. In some embodiments the polyoxyl lipid is HCO-80. In some embodiments the polyoxyl lipid is HCO-100. In some embodiments, the formulation includes a polyalkoxylated alcohol that is octoxynol-40. In some embodiments, the formulation includes a polyalkoxylated alcohol (such as octoxynol-40) present between 0.002 and 4%; or between 0.005 and 3%; or 0.005 and 2%; or 0.005 and 1%; or 0.005 and 0.5%; or 0.005 and 0.1%; or 0.005 and 0.05%; or 0.008 and 0.02%; or about 0.01% by weight of the formulation.

[0047] In some embodiments, the pharmaceutically acceptable excipient is selected from one or more of polyoxyl lipid, fatty acid, and a polyalkoxylated alcohol. In some embodiments, pharmaceutically acceptable excipient is polyoxyl lipid or fatty acid. In some embodiments, the pharmaceutically acceptable excipient is polyalkoxylated alcohol.

[0048] In some embodiments, the pharmaceutical composition includes an active agent (e.g., a compound with structure of any one of Formulae (Γ) or (Γa)-(Γh)), a polyoxyl lipid or fatty acid and a polyalkoxylated alcohol. In some embodiments the polyoxyl lipid or fatty acid is a polyoxyl castor oil. In some embodiments, the polyoxyl lipid or fatty acid is one or more
selected from HCO-40, HCO-60, HCO-80 or HCO-100. In some embodiments the polyoxyl lipid or fatty acid (such as a polyoxyl castor oil such as HCO-40, HCO-60, HCO-80 or HCO-100) is present between 1 and 6%; or 2 and 6%; or 2 and 6%; or 3 and 6%; or 4 and 6%; or 2 and 5%; or 3 and 5%; or 2 and 6%; or about 4%; or greater than 0.7%; or greater than 1%, or greater than 1.5%; or greater than 2%; or greater than 3%; or greater than 4% by weight of the pharmaceutical composition. In some embodiments the polyoxyl lipid is HCO-60. In some embodiments the polyoxyl lipid is HCO-80. In some embodiments the polyoxyl lipid is HCO-100. In some embodiments, the pharmaceutical composition includes a polyalkoxylated alcohol that is octoxynol-40. In some embodiments, the pharmaceutical composition includes a polyalkoxylated alcohol (such as octoxynol-40) present between 0.002 and 4%; or between 0.005 and 3%; or 0.005 and 2%; or 0.005 and 1%; or 0.005 and 0.5%; or 0.005 and 0.1%; or 0.005 and 0.05%>; or 0.008 and 0.02%>; or about 0.01% by weight of the pharmaceutical composition.

[0049] In some embodiments, there is provided an pharmaceutical composition including an active agent, and a n≥ 40 polyoxyl lipid or fatty acid. In some embodiments the polyoxyl lipid or fatty acid is a polyoxyl castor oil. In some embodiments, the polyoxyl lipid or fatty acid is one or more selected from HCO-40, HCO-60, HCO-80 or HCO-100. In some embodiments the polyoxyl lipid or fatty acid (such as a polyoxyl castor oil such as HCO-40, HCO-60, HCO-80 or HCO-100) is present between 0.5 and 2%, or 0.7 and 2%, or 1 and 6%; or 2 and 6%; or 2 and 6%; or 3 and 6%; or 4 and 6%; or 2 and 5%; or 3 and 5%; or 2 and 6%; or about 4%; or greater than 0.7%; or greater than 1%, or greater than 1.5%; or greater than 2%; or greater than 3%; or greater than 4% by weight of the formulation. In some embodiments the polyoxyl lipid is HCO-60. In some embodiments the polyoxyl lipid is HCO-80. In some embodiments the polyoxyl lipid is HCO-100. In some embodiments, the pharmaceutical composition further includes polyalkoxylated alcohol. In some embodiments, the pharmaceutical composition further includes polyalkoxylated alcohol that is octoxynol-40. In some embodiments, the pharmaceutical composition includes a polyalkoxylated alcohol (such as octoxynol-40) present between 0.002 and 4%; or between 0.005 and 3%; or between 0.005 and 2%; or between 0.005 and 1%; or between 0.005 and 0.5%; or between 0.005 and 0.1%; or between 0.005 and 0.05%; or between 0.008 and 0.02%; or between 0.01 and 0.1%; or between 0.02 and 0.08%; or between 0.005 and 0.08%; or about 0.05%, or about 0.01% by weight of the pharmaceutical composition.
In some embodiments, there is provided a pharmaceutical composition that includes an active ingredient (e.g., a compound with structure of any one of Formulae (Γ) or (Γa)-(Γh)) and a polyoxyl lipid or fatty acid; wherein the polyoxyl lipid or fatty acid is present in an amount equal to or greater than 1% of said formulation. In some embodiments, there is provided a pharmaceutical composition that includes an active ingredient and a polyoxyl lipid or fatty acid; wherein said polyoxyl lipid or fatty acid is present in an amount equal to or greater than 0.05% of said formulation. In some embodiments, the polyoxyl lipid or fatty acid is one or more selected from HCO-40, HCO-60, HCO-80 or HCO-100. In some embodiments the polyoxyl lipid or fatty acid (such as a polyoxyl castor oil such as HCO-60, HCO-80 or HCO-100) is present between 0.5 and 2%, or 0.7 and 2%, or between 1 and 6%; or 2 and 6%; or 2 and 6%; or 3 and 6%; or 4 and 6%; or 2 and 5%; or 3 and 5%; or 3 and 5%; or 2 and 6%; or about 4%; or greater than 1.5%; or greater than 2%; or greater than 3%; or greater than 4% by weight of the pharmaceutical composition. In some embodiments the polyoxyl lipid is HCO-40. In some embodiments the polyoxyl lipid is HCO-60. In some embodiments the polyoxyl lipid is HCO-80. In some embodiments the polyoxyl lipid is HCO-100. In some embodiments, the pharmaceutical composition further includes polyalkoxylated alcohol. In some embodiments, the pharmaceutical composition further includes polyalkoxylated alcohol that is octoxynol-40. In some embodiments, the pharmaceutical composition includes a polyalkoxylated alcohol (such as octoxynol-40) present between 0.002 and 4%; or between 0.005 and 3%; or between 0.005 and 2%; or between 0.005 and 1%; or between 0.005 and 0.5%; or between 0.005 and 0.1%; or between 0.005 and 0.05%; or between 0.008 and 0.02%; or between 0.01 and 0.1%; or between 0.02 and 0.08%; or between 0.005 and 0.08%; or about 0.05%, or about 0.01% by weight of the pharmaceutical composition.

In some embodiments the pharmaceutical composition further includes nanomicelles.
or between 0.05 and 5%; or between 0.05 and 0.5%; or between 0.05 and 0.2%, or between 0.08 and 0.12%; or between 0.1 and 0.5%; or between 0.5 and 1%; or between 0.5 and 1.5%; or between 1 and 5%; or between 2 and 4%; or between 4 and 6% of the pharmaceutical composition and is present in nanomicelles of the pharmaceutical composition. In aspects and embodiments, the pharmaceutical compositions of the disclosure are surprisingly effective in dissolving and/or delivering active ingredients (such as hydrophobic active ingredients) without a need for organic solvents (such as propylene glycol) that can be an irritant when included in ophthalmic pharmaceutical compositions. In some embodiments, the pharmaceutical compositions of the present disclosure are surprisingly stable at high temperatures, for example, temperatures above about 40 degrees C. In some aspects and embodiments the nanomicellar nature of some pharmaceutical compositions described herein allow for improved ocular tissue distribution. In certain aspects and embodiments, pharmaceutical compositions as described herein are particularly suitable for anterior eye delivery, or posterior eye delivery, or anterior and posterior eye delivery. Moreover, the pharmaceutical compositions of certain aspects and embodiments of the disclosure may have the surprising advantage of being adaptable to facilitate delivery of active agents having various sizes or properties; for example, in certain embodiments in pharmaceutical compositions that include a polyoxyl castor oil, HCO-60 could be used for active agents having relatively small molecule sizes and HCO-80 and/or HCO-100 could be used for relatively larger sized active agents.

[0052] In some embodiments, there is provided a pharmaceutical composition that includes an active agent and a polyoxyl lipid or fatty acid; wherein the pharmaceutical composition includes nanomicelles. In some embodiments the polyoxyl lipid or fatty acid is a polyoxyl castor oil. In some embodiments the polyoxyl lipid or fatty acid (such as a polyoxyl castor oil such as HCO-40, HCO-60, HCO-80 or HCO-100) is present between 0.5 and 2%, or 0.7 and 2%, or between 1 and 6%; or 2 and 6%; or 2 and 6%; or 3 and 6%; or 4 and 6%; or 2 and 5%; or 3 and 5%; or 3 and 5%; or 2 and 6%; or about 4%; or greater than 0.7%; or greater than 1%, or greater than 1.5%; or greater than 2%; or greater than 3%; or greater than 4% by weight of the pharmaceutical composition. In some embodiments the polyoxyl lipid is HCO-40. In some embodiments the polyoxyl lipid is HCO-60. In some embodiments the polyoxyl lipid is HCO-80. In some embodiments the polyoxyl lipid is HCO-100. In some embodiments, the pharmaceutical composition further includes polyalkoxylated alcohol. In some embodiments, the
pharmaceutical composition further includes polyalkoxylated alcohol that is octoxynol-40. In some embodiments, the pharmaceutical composition includes a polyalkoxylated alcohol (such as octoxynol-40) present between 0.002 and 4%; or between 0.005 and 3%; or between 0.005 and 2%; or between 0.005 and 1%; or between 0.005 and 0.5%; or between 0.005 and 0.1%; or between 0.005 and 0.05%; or between 0.008 and 0.02%; or between 0.01 and 0.1%; or between 0.02 and 0.08%; or between 0.005 and 0.08%; or about 0.05%, or about 0.01% by weight of the formulation.

[0053] In some embodiments, the pharmaceutical composition includes an active agent, 1-5% of one or more selected from the group consisting of HCO-40, HCO-60, HCO-80 and HCO-100; and about 0.01% octoxynol-40.

[0054] In some embodiments, the pharmaceutical composition includes an active agent, 1-5% of one or more selected from the group consisting of HCO-40, HCO-60, HCO-80 and HCO-100; and about 0.01% octoxynol-40.

[0055] In some embodiments, the pharmaceutical composition includes an active agent, about 4% of HCO-60 and about 0.01% octoxynol-40.

[0056] In some embodiments, the pharmaceutical composition includes an active agent, 0.7-1.5% of one or more selected from the group consisting of HCO-40, HCO-60, HCO-80 and HCO-100; and about 0.05% octoxynol-40.

[0057] In some embodiments, the pharmaceutical composition includes an active agent, about 1% of HCO-60 and about 0.05% octoxynol-40.

[0058] In some embodiments, the pharmaceutical composition includes a polyoxyl lipid or fatty acid. In some embodiments the polyoxyl lipid or fatty acid is a polyoxyl castor oil. In some embodiments, the polyoxyl lipid or fatty acid is one or more selected from HCO-40, HCO-60, HCO-80 or HCO-100. In some embodiments the polyoxyl lipid or fatty acid (such as a polyoxyl castor oil such as HCO-60, HCO-80 or HCO-100) is present between 0.5 and 2%, or 0.7 and 2%, or 1 and 6%; or 2 and 6%; or 2 and 6%; or 3 and 6%; or 4 and 6%; or 2 and 5%; or 3 and 5%; or 3 and 5%; or 2 and 6%; or about 4%; or greater than 0.7%; or greater than 1%, or greater than 1.5%; or greater than 2%; or greater than 3%; or greater than 4% by weight of the pharmaceutical composition. In some embodiments the polyoxyl lipid is HCO-40. In some...
embodiments the polyoxyl lipid is HCO-60. In some embodiments the polyoxyl lipid is HCO-80. In some embodiments the polyoxyl lipid is HCO-100.

[0059] In some embodiments, the pharmaceutical composition includes a polyalkoxylated alcohol. In some embodiments, the pharmaceutical composition includes a polyalkoxylated alcohol that is octoxynol-40. In some embodiments, the formulation includes a polyalkoxylated alcohol (such as octoxynol-40) present between 0.002 and 4%; or between 0.005 and 3%; or between 0.005 and 2%; or between 0.005 and 1%; or between 0.005 and 0.5%; or between 0.005 and 0.1%; or between 0.005 and 0.05%; or between 0.008 and 0.02%; or between 0.01 and 0.1%; or between 0.02 and 0.08%; or between 0.005 and 0.08%; or about 0.05%, or about 0.01% by weight of the pharmaceutical composition.

[0060] In some embodiments of the compositions and methods disclosed herein, the active agent includes a combination of two or more different active ingredients. In some embodiments the active agent includes two or more active agents selected from the group consisting of a compound with structure of any one of Formulae (Γ) or (Γα)-(Γθ), resolvin or resolvin-like compound, a steroid (such as a corticosteroid), cyclosporine A, and voclosporin. In some embodiments the active agent includes a resolvin and cyclosporine A. In some embodiments the active agent includes cyclosporine A and a corticosteroid. In some embodiments, the active agent includes a resolvin, cyclosporine A and a corticosteroid. In some embodiments, the active agent includes two or more active agents and one of said active agents is an antibiotic, for example one or more antibiotics selected from the group consisting of azythromycin, ciprofloxacin, ofloxacin, gatifloxacin, levofloxacin, moxifloxacin, besifloxacin, and levofloxacin. In some embodiments, the active agent includes two or more active agents and one of the active agents is an antibiotic, for example one or more antibiotics selected from the group consisting of azythromycin, ciprofloxacin, ofloxacin, gatifloxacin, levofloxacin, moxifloxacin, besifloxacin, and levofloxacin; and a second of such agents is a resolvin such as described herein (including without limitation compound 1001). In some embodiments, the active agent includes two or more active agents and one of said active agents is an antiviral, for example one or more antivirals selected from the group consisting of ganciclovir, trifluridine, acyclovir, famciclovir, valacyclovir, penciclovir and cidofovir. In some embodiments, the active agent includes two or more active agents and one of the active agents is an antibiotic, for example one or more...
antivirals selected from the group consisting of ganciclovir, trifluridine, acyclovir, famciclovir, valacyclovir, penciclovir and cidofovir; and a second of the active agents is a resolvin such as described herein.

[0061] The compositions of the present disclosure may also contain other components such as, but not limited to, additives, adjuvants, buffers, tonicity agents, bioadhesive polymers, and preservatives. In any of the compositions of this disclosure for topical to the eye, the mixtures are preferably formulated at about pH 5 to about pH 8. This pH range may be achieved by the addition of buffers to the composition as described in the examples. In an embodiment, the pH range in the composition in a formulation is about pH 6.6 to about pH 7.0. It should be appreciated that the compositions of the present disclosure may be buffered by any common buffer system such as phosphate, borate, acetate, citrate, carbonate and borate-polyol complexes, with the pH and osmolality adjusted in accordance with well-known techniques to proper physiological values. The mixed micellar compositions of the present disclosure are stable in buffered aqueous solution. That is, there is no adverse interaction between the buffer and any other component that would cause the compositions to be unstable.

[0062] Tonicity agents include, for example, mannitol, sodium chloride, xylitol, etc. These tonicity agents may be used to adjust the osmolality of the compositions. In one aspect, the osmolality of the formulation is adjusted to be in the range of about 250 to about 350 mOsmol/kg. In a preferred aspect, the osmolality of the formulation is adjusted to between about 280 to about 300 mOsmol/kg.

[0063] An additive such as a sugar, a glycerol, and other sugar alcohols, can be included in the compositions of the present disclosure. Pharmaceutical additives can be added to increase the efficacy or potency of other ingredients in the composition. For example, a pharmaceutical additive can be added to a composition of the present disclosure to improve the stability of the calcineurin inhibitor or mTOR inhibitor, to adjust the osmolality of the composition, to adjust the viscosity of the composition, or for another reason, such as effecting drug delivery. Non-limiting examples of pharmaceutical additives of the present disclosure include sugars, such as, trehalose, mannose, D-galactose, and lactose. In an embodiment, the sugars can be incorporated into a composition prior to hydrating the thin film (i.e., internally). In another embodiment, the sugars can be incorporated into a composition during the hydration step (i.e., externally) (see Example
17). In an embodiment, an aqueous, clear, mixed micellar solution of the present disclosure includes additives such as sugars.

[0064] In some embodiments, compositions of the present disclosure further comprise one or more bioadhesive polymers. Bioadhesion refers to the ability of certain synthetic and biological macromolecules and hydrocolloids to adhere to biological tissues. Bioadhesion is a complex phenomenon, depending in part upon the properties of polymers, biological tissue, and the surrounding environment. Several factors have been found to contribute to a polymer’s bioadhesive capacity: the presence of functional groups able to form hydrogen bridges (—OH, COOH), the presence and strength of anionic charges, sufficient elasticity for the polymeric chains to interpenetrate the mucous layer, and high molecular weight. Bioadhesive systems have been used in dentistry, orthopedics, ophthalmology, and in surgical applications. However, there has recently emerged significant interest in the use of bioadhesive materials in other areas such as soft tissue-based artificial replacements, and controlled release systems for local release of bioactive agents. Such applications include systems for release of drugs in the buccal or nasal cavity, and for intestinal or rectal administration.

[0065] In an embodiment, a composition of the present disclosure includes at least one bioadhesive polymer. The bioadhesive polymer can enhance the viscosity of the composition and thereby increase residence time in the eye. Bioadhesive polymers of the present disclosure include, for example, carboxylic polymers like CARBOPOL® (carbomers), NOVEON® (polycarbophil), cellulose derivatives including alkyl and hydroxyalkyl cellulose like methylcellulose, hydroxypropylcellulose, carboxymethylcellulose, gums like locust bean, xanthan, agarose, karaya, guar, and other polymers including but not limited to polyvinyl alcohol, polyvinyl pyrrolidone, polyethylene glycol, PLURONIC® (Poloxamers), tragacanth, and hyaluronic acid; phase-transition polymers for providing sustained and controlled delivery of enclosed medicaments to the eye (e.g., alginic acid, carrageenans (e.g., Eucheuma), xanthan and locust bean gum mixtures, pectins, cellulose acetate phthalate, alkylhydroxyalkyl cellulose and derivatives thereof, hydroxyalkylated polyacrylic acids and derivatives thereof, poloxamers and their derivatives, etc. Physical characteristics in these polymers can be mediated by changes in environmental factors such as ionic strength, pH, or temperature alone or in combination with other factors. In an embodiment, the optional one or more bioadhesive polymers is present in the
composition from about 0.01 wt % to about 10 wt %/volume, preferably from about 0.1 to about 5 wt %/volume. In an embodiment, the compositions of the present disclosure further comprise at least one hydrophilic polymer excipient selected from, for example, PVP-K-30, PVP-K-90, HPMC, HEC, and polycarbophil. In an embodiment, the polymer excipient is selected from PVP-K-90, PVP-K-30 or HPMC. In an embodiment, the polymer excipient is selected from PVP-K-90 or PVP-K-30.

[0066] In an embodiment, if a preservative is desired, the compositions may optionally be preserved with any of many well-known preservatives, including benzyl alcohol with/without EDTA, benzalkonium chloride, chlorhexidine, COSMOCIL® CQ, or DOWICIL® 200. In some embodiments, it may be desirable for a formulation as described herein to not include any preservatives. In this regard, preservatives may in some embodiments not be necessary or desirable in formulations included in single use containers. In other embodiments it may be advantageous to include preservatives, such as in certain embodiments in which the formulations are included in a multiuse container.

[0067] The pharmaceutical compositions can be administered topically to the eye as biocompatible, aqueous, clear mixed micellar solutions. The compositions have the drugs incorporated and/or encapsulated in micelles which are dispersed in an aqueous medium.

BRIEF DESCRIPTION OF THE DRAWINGS

[0068] Figures 1A-1F. Representative slit-lamp photographs of subepithelial haze and immunohistochemistry for myoblast marker alpha-smooth muscle actin in rabbits. Figure 1A: Moderate to severe (grade 3) haze (arrows) was noted in a vehicle control group cornea. Figure IB: Grade 2 subepithelial haze was observed in a rabbit eye that was treated with 0.01% resolvin E1. Figure 1C: Faint subepithelial grade 0.5 haze was seen in a rabbit treated with 0.1% resolvin E1. El. Magnification 10x.

[0069] Figures 1D-1F present representative images of immunohistochemical staining for the a-smooth muscle actin (SMA) marker for myofibroblasts in the central cornea of rabbit eyes in groups treated with vehicle control solution (Figure 1D), 0.01%> resolvin E1 (Figure 1E), and 0.1% resolvin E1 (Figure 1F) at 4 weeks after -9D PRK. Cell nuclei are stained blue with 4’, 6-
diamidino-2-phenylindole (DAPI) and SMA+ cells are stained red (arrows). e=epithelium. Magnification 400X.

[0070] Figures 2A-2C. Representative images of immunohistochemical staining for the alpha-smooth muscle actin (SMA) marker for myofibroblasts in the central cornea of rabbit eyes in groups treated with (Figure 2A) vehicle control solution, (Figure 2B) 0.01% resolvin E1, and (Figure 2C) 0.1% resolvin E1 at four weeks after -9D PRK. Cell nuclei are stained blue with DAPI and SMA+ cells are stained (arrows). Magnification 400x.

[0071] Figure 3 demonstrates that resolvin E1 reduces PCO in an ex vivo canine model. Lens capsules were graded in which a percent confluence was assigned to each capsule for each observational time point. Beginning on day 5, vehicle-treated capsules had significantly more LEC present compared to capsules treated with RX-10045.

[0072] Figures 4A-4C provide representative images demonstrating reduced presence of LEC in the anterior and posterior capsule of resolvin E1 treated eyes. In each set of photomicrographs, the top section (above the dashed line) is more peripheral in the capsule and both anterior, "a", and posterior, "p", capsule can be visualized. Below the dashed line, only the central capsule is depicted; only the posterior capsule is viewed. Figure 4A depicts a control capsule. LEC, as highlighted with arrows, populate the anterior and posterior capsule in both the central and peripheral axis. Figure 4B depicts capsules treated with 0.1% RX-10045. LEC are confined to the peripheral capsule and were absent centrally. The remaining LEC were frequently abnormal and appeared pyknotic, as shown in the higher magnification inset. Figure 4C depicts capsules treated with 0.5% RX-10045—and demonstrates a paucity of LEC on both anterior and posterior capsules in the central and peripheral axis.

DETAILED DESCRIPTION OF THE INVENTION

[0073] The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

[0074] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., -CH₂0⁻ is equivalent to -OCH₂⁻.
As used herein, the term "polyoxyl lipid or fatty acid" refers to mono- and diesters of lipids or fatty acids and polyoxyethylene diols. Polyoxyl lipids or fatty acids may be numbered ("n") according to the average polymer length of the oxyethylene units (e.g., 40, 60, 80, 100) as is well understood in the art. The term "n ≥ 40 polyoxyl lipid" means that the polyoxyl lipid or fatty acid has an average oxyethylene polymer length equal to or greater than 40 units. Stearate hydrogenated castor oil and castor oil are common lipids/fatty acids commercially available as polyoxyl lipids or fatty acid, however, it is understood that any lipid or fatty acid could polyoxylated to become a polyoxyl lipid or fatty acid as contemplated herein. Examples of polyoxyl lipid or fatty acids include without limitation HCO-40, HCO-60, HCO-80, HCO-100, polyoxyl 40 stearate, polyoxyl 35 castor oil. In some embodiments of any of the pharmaceutical compositions and methods described herein, the average polymer length of the oxyethylene units of a polyoxyl lipid or fatty acid is longer for a relatively larger active ingredient and is shorter for a relatively smaller active ingredient; for example in some embodiments in which the active ingredient is a resolvin or resolvin-like compound the polyoxyl lipid is HCO-60 and in some embodiments where the active ingredient is cyclosporine A (which is larger than a resolvin) the polyoxyl lipid is HCO-80 or HCO-100.

As used herein, the term "micelle" or "nanomicelle" refers to an aggregate (or cluster) of surfactant molecules. Micelles only form when the concentration of surfactant is greater than the critical micelle concentration (CMC). Surfactants are chemicals that are amphipathic, which means that they contain both hydrophobic and hydrophilic groups. Micelles can exist in different shapes, including spherical, cylindrical, and discoidal. A micelle comprising at least two different molecular species is a mixed micelle. In embodiments, pharmaceutical compositions of the present disclosure include an aqueous, clear, mixed micellar solution.

The term "acyl" is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)-, preferably alkylC(O)-.

The term "acylamino" is art-recognized and refers to an amino group substituted with an acyl group and may be represented, for example, by the formula hydrocarbylC(0)NH-.

The term "acyloxy" is art-recognized and refers to a group represented by the general formula hydrocarbylC(0)O-, preferably alkylC(0)O-.
The term "alkoxy" refers to an alkyl group, preferably a lower alkyl group, having an oxygen attached thereto. Representative alkoxy groups include methoxy, ethoxy, propoxy, tert-butoxy and the like.

The term "alkoxyalkyl" refers to an alkyl group substituted with an alkoxy group and may be represented by the general formula alkyl-O-alkyl.

The term "alkenyl", as used herein, refers to an aliphatic group containing at least one double bond and is intended to include both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the alkenyl group. Such substituents may occur on one or more carbons that are included or not included in one or more double bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed below, except where stability is prohibitive. For example, substitution of alkenyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

The term "alkyl" refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl-substituted cycloalkyl groups, and cycloalkyl-substituted alkyl groups. In preferred embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C1-C30 for straight chains, C3-C30 for branched chains), and more preferably 20 or fewer. Likewise, preferred cycloalkyls have from 3-10 carbon atoms in their ring structure, and more preferably have 5, 6 or 7 carbons in the ring structure.

Moreover, the term "alkyl" (or "lower alkyl") as used throughout the specification, examples, and claims is intended to include both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents, if not otherwise specified, can include, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxy carbonyl, a formyl, or an acyl), a thio carbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphinate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the
hydrocarbon chain can themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), -CF₃, -CN and the like. Exemplary substituted alkyls are described below. Cycloalkyls can be further substituted with alkyls, alkenyls, alkoxy, alkynyls, aminoalkyls, carbonyl-substituted alkyls, -CF₃, -CN, and the like.

0085 The term "Cₓᵧ" when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from x to y carbons in the chain. For example, the term "Cₓᵧalkyl" refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from x to y carbons in the chain, including haloalkyl groups such as trifluoromethyl and 2,2,2-tirfluoroethyl, etc. Co alkyl indicates a hydrogen where the group is in a terminal position, a bond if internal. The terms "C₂ₓᵧalkenyl" and "C₂ₓᵧalkynyl" refer to substituted or unsubstituted unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

0086 The term "alkylamino", as used herein, refers to an amino group substituted with at least one alkyl group.

0087 The term "alkylthio", as used herein, refers to a thiol group substituted with an alkyl group and may be represented by the general formula alkylS⁻.

0088 The term "alkynyl", as used herein, refers to an aliphatic group containing at least one triple bond and is intended to include both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the alkynyl group. Such substituents may occur on one or more carbons that are included or not included in one or more triple bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed above, except where stability is prohibitive. For example, substitution of alkynyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

0089 The term "amide", as used herein, refers to a group
wherein each \( R^{10} \) independently represent a hydrogen or hydrocarbyl group, or two \( R^{10} \) are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

[0090] The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines and salts thereof, e.g., a moiety that can be represented by

\[
\begin{align*}
\text{R}_{10}^1 & \quad \text{N} \quad \text{R}_{10}^1 \\
\text{R}_{10}^2 & \quad \text{N} \quad \text{R}_{10}^2
\end{align*}
\]

wherein each \( R^{10} \) independently represents a hydrogen or a hydrocarbyl group, or two \( R^{10} \) are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

[0091] The term "aminoalkyl", as used herein, refers to an alkyl group substituted with an amino group.

[0092] The term "aralkyl", as used herein, refers to an alkyl group substituted with an aryl group.

[0093] The term "aryl" as used herein include substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. Preferably the ring is a 5- to 7-membered ring, more preferably a 6-membered ring. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyals, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like.

[0094] The term "carbamate" is art-recognized and refers to a group

\[
\begin{align*}
\text{O} & \quad \text{N} \quad \text{R}^{10} \\
\text{O} & \quad \text{N} \quad \text{R}^{10}
\end{align*}
\]
wherein R⁹ and R¹⁰ independently represent hydrogen or a hydrocarbyl group, such as an alkyl group, or R⁹ and R¹⁰ taken together with the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

[0095] The terms "carbocycle", "carbocyclyl", and "carbocyclic", as used herein, refers to a non-aromatic saturated or unsaturated ring in which each atom of the ring is carbon. Preferably a carbocycle ring contains from 3 to 10 atoms, more preferably from 5 to 7 atoms.

[0096] The term "carbocyclylalkyl", as used herein, refers to an alkyl group substituted with a carbocycle group.

[0097] The term "carbonate" is art-recognized and refers to a group -OCO₂-R¹⁰, wherein R¹⁰ represents a hydrocarbyl group.

[0098] The term "carboxy", as used herein, refers to a group represented by the formula -CO₂H.

[0099] The term "ester", as used herein, refers to a group -C(0)OR¹⁰ wherein R¹⁰ represents a hydrocarbyl group.

[0100] The term "ether", as used herein, refers to a hydrocarbyl group linked through an oxygen to another hydrocarbyl group. Accordingly, an ether substituent of a hydrocarbyl group may be hydrocarbyl-O-. Ethers may be either symmetrical or unsymmetrical. Examples of ethers include, but are not limited to, heterocycle-O-heterocycle and aryl-O-heterocycle. Ethers include "alkoxyalkyl" groups, which may be represented by the general formula alkyl-O-alkyl.

[0101] The terms "halo" and "halogen" as used herein means halogen and includes chloro, fluoro, bromo, and iodo.

[0102] The terms "hetaralkyl" and "heteroaralkyl", as used herein, refers to an alkyl group substituted with a hetaryl group.

[0103] The term "heteroalkyl", as used herein, refers to a saturated or unsaturated chain of carbon atoms and at least one heteroatom, wherein no two heteroatoms are adjacent.

[0104] The terms "heteroaryl" and "hetaryl" include substituted or unsubstituted aromatic single ring structures, preferably 5- to 7-membered rings, more preferably 5- to 6-membered
rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heteroaryl" and "hetaryl" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heteroaromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like.

[0105] The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, and sulfur.

[0106] The terms "heterocyclyl", "heterocycle", and "heterocyclic" refer to substituted or unsubstituted non-aromatic ring structures, preferably 3- to 10-membered rings, more preferably 3- to 7-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heterocyclyl" and "heterocyclic" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heterocyclic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyls. Heterocyclyl groups include, for example, piperidine, piperazine, pyrrolidine, morpholine, lactones, lactams, and the like.

[0107] The term "heterocyclylalkyl", as used herein, refers to an alkyl group substituted with a heterocycle group.

[0108] The term "hydrocarbyl", as used herein, refers to a group that is bonded through a carbon atom that does not have a =O or =S substituent, and typically has at least one carbon-hydrogen bond and a primarily carbon backbone, but may optionally include heteroatoms. Thus, groups like methyl, ethoxyethyl, 2-pyridyl, and trifluoromethyl are considered to be hydrocarbyl for the purposes of this application, but substituents such as acetyl (which has a =O substituent on the linking carbon) and ethoxy (which is linked through oxygen, not carbon) are not. Hydrocarbyl groups include, but are not limited to aryl, heteroaryl, carbocycle, heterocycle, alkyl, alkenyl, alkynyl, and combinations thereof.
The term "hydroxyalkyl", as used herein, refers to an alkyl group substituted with a hydroxy group.

The term "lower" when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups where there are ten or fewer non-hydrogen atoms in the substituent, preferably six or fewer. A "lower alkyl", for example, refers to an alkyl group that contains ten or fewer carbon atoms, preferably six or fewer. In some embodiments, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy substituents defined herein are respectively lower acyl, lower acyloxy, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy, whether they appear alone or in combination with other substituents, such as in the recitations hydroxyalkyl and aralkyl (in which case, for example, the atoms within the aryl group are not counted when counting the carbon atoms in the alkyl substituent).

A "size-limited substituent" or "size-limited substituent group," as used herein, means a group wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C1-C20 (e.g., C1-C2, C1-C3, C1-C4, C1-C5, C1-C6, C1-C7, C1-C8, C1-C9, C1-C10, C1-C11, C1-C12, C1-C13, C1-C14, C1-C15, C1-C16, C1-C17, C1-C18, C1-C19, C1-C20) alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C4-C8 cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 4 to 8 membered heterocycloalkyl.

The terms "polycyclic", "polycycle", and "polycyclic" refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls) in which two or more atoms are common to two adjoining rings, e.g., the rings are "fused rings". Each of the rings of the polycycle can be substituted or unsubstituted. In some embodiments, each ring of the polycycle contains from 3 to 10 atoms in the ring, preferably from 5 to 7.

The term "silyl" refers to a silicon moiety with three hydrocarbyl moieties attached thereto.

The term "substituted" refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence
of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxy carbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclic, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. Unless specifically stated as "unsubstituted," references to chemical moieties herein are understood to include substituted variants. For example, reference to an "aryl" group or moiety implicitly includes both substituted and unsubstituted variants.

[0115] The term "sulfate" is art-recognized and refers to the group -OSO₂H, or a pharmaceutically acceptable salt thereof.

[0116] The term "sulfonamide" is art-recognized and refers to the group represented by the general formulae

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{R}^9 & \quad \text{R}^{10}
\end{align*}
\] or

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{R}^9 & \quad \text{R}^{10}
\end{align*}
\]

wherein R⁹ and R¹⁰ independently represents hydrogen or hydrocarbyl, such as alkyl, or R⁹ and R¹⁰ taken together with the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.
The term "sulfoxide" is art-recognized and refers to the group \(-\text{S}(0)\)-R\(^{10}\), wherein R\(^{10}\) represents a hydrocarbyl.

The term "sulfonate" is art-recognized and refers to the group SO\(_3\)H, or a pharmaceutically acceptable salt thereof.

The term "sulfone" is art-recognized and refers to the group \(-\text{S}(0)\)_2-R\(^{10}\), wherein R\(^{10}\) represents a hydrocarbyl.

The term "thioalkyl", as used herein, refers to an alkyl group substituted with a thiol group.

The term "thioester", as used herein, refers to a group \(-\text{C}(0)\text{SR}^{10}\) or \(-\text{SC}(0)\text{R}^{10}\) wherein R\(^{10}\) represents a hydrocarbyl.

The term "thioether", as used herein, is equivalent to an ether, wherein the oxygen is replaced with a sulfur.

The term "urea" is art-recognized and may be represented by the general formula

\[
\text{\(\begin{array}{c}
\text{N} \\
\text{N} \\
\text{O}
\end{array}\)}
\]  

wherein R\(^9\) and R\(^{10}\) independently represent hydrogen or a hydrocarbyl, such as alkyl, or either occurrence of R\(^9\) taken together with R\(^{10}\) and the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

"Protecting group" refers to a group of atoms that, when attached to a reactive functional group in a molecule, mask, reduce or prevent the reactivity of the functional group. Typically, a protecting group may be selectively removed as desired during the course of a synthesis. Examples of protecting groups can be found in Greene and Wuts, Protective Groups in Organic Chemistry, 3\(^{rd}\) Ed., 1999, John Wiley & Sons, NY and Harrison et al, Compendium of Synthetic Organic Methods, Vols. 1-8, 1971-1996, John Wiley & Sons, NY. Representative nitrogen protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxy carbonyl ("CBZ"), tert-butoxycarbonyl ("Boc"), trimethylsilyl ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("TES"), trityl and substituted trityl groups, allyloxy carbonyl, 9-fluorenymethyloxycarbonyl ("FMOC"), nitro-veratryloxycarbonyl ("NVOC") and the like.
Representative hydroxylprotecting groups include, but are not limited to, those where the hydroxyl group is either acylated (esterified) or alkylated such as benzyl and trityl ethers, as well as alkyl ethers, tetrahydropyranyl ethers,trialkylsilyl ethers (e.g., TMS or TIPS groups), glycol ethers, such as ethylene glycol and propylene glycol derivatives and allyl ethers.

[0125] The terms "subject," "patient," "subject in need thereof" and the like refer to a living organism suffering from or prone to a disease or condition that can be treated by administration of a compound or pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a subject is human.

[0126] An "effective amount" is an amount sufficient to accomplish a stated purpose (e.g., to achieve the effect for which it is administered, treat a disease, treat, reduce or prevent ocular fibrosis, reduce one or more symptoms of a disease or condition, and the like). An example of an "effective amount," "therapeutically effective amount" or the like is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease. A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s).

[0127] The terms "treat," "treating" and the like refer to preventing a disease, disorder or condition from occurring in a cell, a tissue, a system, animal or human which may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having it; stabilizing a disease, disorder or condition, i.e., arresting its development; and/or relieving one or more symptoms of the disease, disorder or condition, i.e., causing regression of the disease, disorder and/or condition.

[0128] The terms "preventing," "prevention" and the like as used herein in the context of ocular fibrosis refer, in the usual and customary sense, to prophylactic intervention to reduce, delay or forestall the onset or reoccurrence of an injury, disease, pathology or condition, or reducing the likelihood of the onset or reoccurrence of an injury, disease, pathology, or condition, or symptoms thereof. A "prophylactically effective amount" of a drug (e.g., a compound disclosed herein useful for medical or veterinary indications) is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing
the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An "activity decreasing amount," as used herein, refers to an amount of a compound disclosed herein required to achieve a desired result, e.g., prevention and treatment of ocular fibrosis of the cornea, lens and lens capsule in a subject in need thereof. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins). As used herein, a therapeutic that prevents a disorder or condition refers to a compound that, in a statistical sample, reduces the occurrence of the disorder or condition in the treated sample relative to an untreated control sample, or delays the onset or reduces the severity of one or more symptoms of the disorder or condition relative to the untreated control sample.

[0129] As used herein, the terms "ocular disease," "ocular condition," "eye disease," and "eye condition" refer to diseases/conditions of the eye(s) that can be sight threatening, lead to eye discomfort, and may signal systemic health problems.

[0130] As used herein, the term "anterior segment disease" refers to all disorders that affect the eye surface, anterior chamber, iris and ciliary body and lens of the eye. The eye surface is composed of the cornea, conjunctiva, eyelids, lacrimal and meibomian glands, and the interconnecting nerves.

[0131] As used herein, the terms "posterior segment eye disease" and "back-of-the-eye disease" refer to all disorders that affect the posterior segment of the eye. A posterior eye disease is a disease which primarily affects a posterior ocular site such as choroid or sclera, vitreous, vitreous chamber, retina, optic nerve, and blood vessels and nerves which vascularize or innervate a posterior ocular site.

[0132] The term "LASIK" refers, in the usual and customary sense, to the surgical procedure laser-assisted in situ keratomileusis, as known in the art. The term "LASEK" refers, in the usual
and customary sense, to the surgical procedure laser-assisted epithelial keratoplasty, as known in the art. The term "PRK" refers, in the usual and customary sense, to the surgical procedure photorefractive keratectomy, as known in the art.

[0133] The term "pharmaceutically acceptable" (e.g., pharmaceutically acceptable salt, pharmaceutically acceptable excipient, and the like) refers, in the usual and customary sense, to pharmaceutically and physiologically acceptable, organic or inorganic carrier substances suitable for enteral or parenteral administration, which substantances do not deleteriously react with the active agent or in a subject undergoing administration, as judged by one of skill in the medical or veterinary arts.

10 Examples

[0134] Example 1. Resolvin E1 Analog RX-10045 0.1% Reduces Corneal Stromal Haze in Rabbits when Applied Topically After PRK.

[0135] There are disclosed herein studies to evaluate the effect of a novel topical formulation of a resolvin E1 analog [RX-10045; (5S,8E,10E,12R)-isopropyl 5,12-hydroxypentadeca-8,10-dien-6,14-diynoate], on haze and myofibroblast generation after haze producing corneal injury (PRK) in rabbits.

[0136] Resolvin RX-10045. RX-10045 is an isopropyl ester pro-drug of the resolvin E1 analog, RX-10008. The chemical structures for RX-10008 and RX-10045 follow:

![Chemical Structures]

RX-10008

RX-10045
[0137] The pro-drug (RX-10045) very rapidly hydrolyzes to its active acid form (RX-10008) in biological matrices. RX-10045 was formulated at a concentration of 0.01% and 0.1% in a novel biocompatible preservative free vehicle which contains mixed polymeric micelles comprising of hydrogenated castor oil-40 and octoxynol-40 to help keep RX-10045 in aqueous solution. Vehicle solution contains mixed polymeric micelles containing no drug. Other additives included common excipients to maintain desirable tonicity, osmolality and a buffering capacity of around pH 5.5. Prepared as an aqueous nanomicellar formulation, it is intended to increase the ocular and periocular tissue concentrations of drug (RX-10008) after ocular administration. Vials of formulated RX-10045 and vehicle were shipped in masked fashion and stored at 4°C until use.

[0138] Animals, surgery, and drug application groups. All animals were treated in accordance with the tenets of the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research, and the Animal Control Committee at the Cleveland Clinic approved these studies.

[0139] Anesthesia was achieved by intramuscular injection of ketamine hydrochloride (30 mg/kg) and xylazine hydrochloride (5 mg/kg). In addition, topical proparacaine hydrochloride 1%, (Alcon, Ft. Worth, TX, USA) was applied to each eye just before surgery.

[0140] Twenty-four 12 to 15 week old female New Zealand white rabbits weighing 2.5-3.0 kg each were included in this study. Haze-generating injury was performed in one cornea of each rabbit by 9 mm diameter epithelial scrape and application of a -9.0D PRK with a VISX S4 IR excimer laser (AMO, Irvine, CA), as previously described (Mohan et al, 2003). One eye of each rabbit selected at random was treated with the masked aliquots of test solutions. The key to masking was held by a neutral party and was not disclosed to the investigators until haze and myofibroblast density data was finalized and tabulated for all of the rabbits. The three groups with eight rabbits each were as follows:

- Group 1 received 30 μ of 0.1% RX-10045 per application.
- Group 2 received 30 μ of 0.01% RX-10045 per application.
- Group 3 received 30 μ of vehicle solution per application.
All drops in each group were given with a Pipetman (Gilson, Inc., Middleton, WI) with sterile tips every four hours beginning immediately after PRK surgery and for five days. The corneal epithelium had closed prior to the last application of test drug in all rabbits. All rabbits were provided with acetaminophen in drinking water at a concentration of 6 mg/ml post-procedure until the epithelium healed at 3 to 5 days after surgery.

Biomicroscopic grading of corneal haze. Treated animal corneas were evaluated at the slit-lamp (Haag-Streit BM900, Haag-Streit, Switzerland) while under general anesthesia and photographed at one month after PRK surgery. Corneal opacity (haze) was graded according to the system reported by Fantes et al. (1990): grade 0 for a completely clear cornea; grade 0.5 for trace haze seen with careful oblique illumination with slit-lamp biomicroscopy; grade 1 for more prominent haze not interfering with visibility of fine iris details; grade 2 for mild obscuration of iris details; grade 3 for moderate obscuration of the iris and lens; and grade 4 for complete opacification of the stroma in the area of the ablation.

Cornea collection, fixation and sectioning. Rabbits were euthanized at one month after PRK with an intravenous Beuthanasia overdose (100 mg/ kg) and the corneoscleral rim was collected without manipulation of the cornea using 0.12 forceps and sharp Westcott scissors. The corneoscleral rims were immediately embedded in liquid OCT compound (Sakura Finetek, Torrance, CA, USA) within a 24 mm x 24 mm x 5 mm mold (Fisher, Pittsburgh, PA). Specimens were centered within the mold so that the block could be bisected and transverse sections cut from the center of the cornea. Frozen tissue blocks were stored at -80° C until sectioning was performed. Central corneal sections (7 µm thick) were cut with a cryostat (HM 505M, Micron GmbH, Walldorf, Germany). Sections were placed on 25 mm x 75 mm x 1 mm microscope slides (SUPERFROST™ Plus, Fisher) and maintained frozen at -80°C until staining was performed.

Immunohistochemistry. Immunohistochemical staining was performed on tissue sections as previously described (Barbosa et al., 2010a). Briefly, sections from the central cornea were stained for a-smooth muscle actin (a-SMA) using a monoclonal mouse anti-human smooth muscle actin cloneA4 (Cat. # M0851, Dako, Carpinteria, CA). The antibody was used on the sections at 1:50 dilution in 1% BSA and incubated at room temperature for 90 minutes. Sections were washed with PBS and then incubated at room temperature for 60 minutes in ALEXA
FLUOR® 568 (Cat. # A1 1031, Invitrogen, Carlsbad, CA) secondary antibody, goat anti-mouse IgG (H + L) (Red) diluted 1:100 in PBS before washing with PBS three times. Immunocytochemical controls were performed by substituting mouse non-specific IgG1 for the primary antibody. Coverslips were mounted with VECTASHIELD™ containing DAPI (Vector Laboratories Inc., Burlingame, CA) to allow visualization of all nuclei in the tissue sections. The sections were viewed and photographed with a Leica DM5000 microscope equipped with Q- Imaging RETIGA™ 4000RV (Surrey, BC, Canada) camera and IMAGE-PRO® software. IHC was performed at least three times on sections from each cornea to assure the consistent result.

Quantification of cells. SMA+ cells were counted real-time at the microscope. SMA+ myofibroblast densities were performed by counting the number of cells per 400x field tangent to the epithelial basement membrane in the central cornea and averaging the counts for seven non-overlapping fields—as previously described (Netto et al, 2006).

Statistical analysis. Data processing and analysis were performed with SPSS version 20.0 software (SPSS, Inc, Chicago, IL). Means and standard deviations of SMA+ myofibroblast density were determined for each group. Comparisons between opacity grades in the treatment groups were evaluated using Mann-Whitney U test. Comparisons between SMA+ counting in the treatment groups were performed using unpaired t-test for continuous variables. A p values less than 0.05 was considered statistically significant.

Effect of RX-10045 on corneal opacity (haze) evaluated by slit lamp biomicroscopy. Corneal opacity was significantly lower in the 0.1% RX-10045 group compared to the vehicle control group (p=0.049) at one month after -9.0D PRK (Figures 1A-1F). There was no significant difference in opacity between the 0.1% RX-10045 group and the 0.01% RX-10045 group (p=0.27) or between the 0.01% RX-10045 group and the vehicle control group (p=0.38). The masked opacity grade for each rabbit cornea is shown in Tables 1 and 2.

Table 1 Haze at Slit Lamp - 1 Month Post Surgery; Masked Grading per Fantes classification

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>RX-10045 0.01%</th>
<th>RX-10045 0.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vial #</td>
<td>Haze</td>
<td>Vial #</td>
</tr>
<tr>
<td>04</td>
<td>2</td>
<td>03</td>
</tr>
<tr>
<td>06</td>
<td>3</td>
<td>05</td>
</tr>
<tr>
<td>07</td>
<td>2</td>
<td>09</td>
</tr>
</tbody>
</table>
Effect of RX-10045 on stromal myofibroblast density. SMA+ myofibroblast cell densities (cells per 400X microscopic field) at one month after -9.0D PRK were not significantly different between the 0.1% RX-10045 group and the vehicle control group (p=0.24), the 0.01% RX-10045 group and vehicle control group (p=0.45), or the 0.1% RX-10045 group and the 0.01% RX-10045 group (p=0.22) (Tables 3 and 4). However, there appeared to be outliers in each group (corneas with fifty or more SMA+ cells/400X field and corneas with virtually no SMA+ cells). Therefore, the data were also analyzed after excluding the highest and lowest SMA+ cell value in each group. With these exclusions, the difference between the 0.1% RX-10045 group and the vehicle control group nearly reached statistical significance (10±10 cells/400X field vs. 18±7 cells/400X field, respectively, p=0.07). Similarly, a stronger trend towards a significant difference was noted between the 0.1% RX-10045 group and the 0.01%
RX-10045 group (10±10 cells/400X field vs. 20±12 cells/400X field, respectively, p=0.08). There was no difference between 0.01% RX-10045 group and the vehicle control group (20±12 cells/400X field vs. 18±7 cells/400X field, respectively, p=0.41).

**Table 3** Myofibroblast Density in the Anterior Corneal Stroma - 1 Month Post -9 diopter PRK.

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>RX-10045 0.01%</th>
<th>RX-10045 0.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vial #</td>
<td>SMA+Cells</td>
<td>Vial #</td>
</tr>
<tr>
<td>04</td>
<td>25</td>
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<td>13</td>
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<tr>
<td>18</td>
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<td>16</td>
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<tr>
<td>19</td>
<td>50c</td>
<td>20</td>
</tr>
<tr>
<td>22</td>
<td>9</td>
<td>24</td>
</tr>
</tbody>
</table>

**Trimmed Mean** c  | 20           | 21           | 14           | 18           | 18           |
| **Std. Dev.** a   | 15           | 17           | 0.410        | 0.070        | 0.080        |
| **p-value** b     | --           | 0.410        |              |              |              |

---

**TABLE 4, ALPHA-SMOOTH MUSCLE ACTIN+ MYOFIBROBLAST DENSITY IN THE ANTERIOR STROMA (SMA+/400X FIELD) AT 1 MONTH AFTER SURGERY.**

<table>
<thead>
<tr>
<th>Rabbit</th>
<th>Group 1 0.1% e</th>
<th>eelvin</th>
<th>Group 2 0.01% Resolvin</th>
<th>Group 3 Vehicle Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>11</td>
<td>2S</td>
<td>2S</td>
</tr>
<tr>
<td>2</td>
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<td>14</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
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<td>1S</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
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<td>1S</td>
<td>1S</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>32</td>
<td>1S</td>
<td>29</td>
</tr>
<tr>
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<td>10</td>
<td>0</td>
<td>9</td>
</tr>
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</tr>
<tr>
<td>f</td>
<td>28</td>
<td>1</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>

**Mean ± SD** 14±18 21±17 28±15

Each value represents the average of seven non-overlapping 400X fields for each cornea. The mean ± the standard deviation is provided for each group.
Resolvins have been characterized as agonists of inflammatory resolution in many ocular and non-ocular inflammatory disorders (Rajasagi et al., 2011; Serhan and Chiang, 2008). The present masked study found that topical 0.1% RX-10045 given immediately after laser application and every four hours for 5 days after opacity-inducing PRK in rabbits decreases haze generation in the cornea at one month after surgery. There was also a trend towards reduced corneal myofibroblast generation that may have reached significance if more eyes had been included in the study.

Li et al (2010) found that resolvin E1 decreased α-SMA+ cell generation in a murine dry eye model. That study also found that resolvin E1 attenuated the influx of cells of macrophage lineage, which suggests that the effect of this regulator may be mediated via differentiation of bone marrow-derived fibrocytes from macrophage precursors or the subsequent differentiation of fibrocytes into myofibroblasts (Abe et al., 2001; Bucala et al., 1994; Mori et al., 2005; Quan, Cowper, and Bucala, et al., 2006; Schmidt et al., 2003). Corneal myofibroblasts may be derived from both bone marrow-derived precursors and keratocyte-derived precursors (Barbosa et al., 2010a; Singh et al., 2014).

Without wishing to be bound by any theory, it is believed that the RX-10045 at least partially blocked myofibroblast generation from bone marrow-derived precursors without substantial effect on myofibroblast generation from keratocyte-derived precursors. If this is the case, then treatment with a compound (or compounds) that modulates both sources of corneal myofibroblasts will be needed to more substantially decrease opacity and myofibroblast generation after haze-inducing injury.

It is encouraging that the RX-10045 effect on corneal haze after PRK was achieved with topical application. In a prior study of PRM-151, a recombinant form of human pentraxin-2 (PTX-2—also referred to as serum amyloid P), that inhibits differentiation of circulating monocytes into fibrocytes and profibrotic macrophages, myofibroblast generation after haze-inducing PRK was modulated only by subconjunctival injection of the compound, not topical application (Santhiago et al., 2011). Presumably, this occurred because of inadequate penetration of PRM-151 into the stroma after topical application. The current study suggests that RvEl does penetrate into the cornea after topical application—at least when an epithelial defect associated
with PRK is present. In the rabbit PRK model used in this study the rabbit epithelium closed approximately 4 days after surgery.

I. Non-Limiting List of Exemplary Embodiments

[0153] In addition to the aspects and embodiments described and provided elsewhere in this disclosure, the following non-limiting list of particular embodiments are specifically contemplated.

[0154] Embodiment 1. A method for the prevention and/or treatment of ocular fibrosis of the cornea, lens and/or lens capsule, the method including administering to a subject in need thereof an effective amount of the compound with structure of Formula (I'):

\[
\begin{align*}
&\text{OH} \\
&\text{R} \\
&\text{O} \\
&\text{R}
\end{align*}
\]

(I’),

wherein:

R is hydrogen or C\textsubscript{i}-C\textsubscript{6} alkyl.

[0155] Embodiment 2. The method of embodiment 1, wherein the ocular fibrosis results from inflammatory cells or by proliferation of fibroblasts or fibroblast-like cells activated as a result of trauma, infection or surgery.

[0156] Embodiment 3. The method of embodiment 2, wherein the surgery is laser-assisted in situ keratomileusis (LASIK), laser-assisted epithelial keratoplasty (LASEK) or photorefractive keratectomy (PRK).

[0157] Embodiment 4. The method of embodiment 3, wherein the surgery is LASIK.

[0158] Embodiment 5. The method of embodiment 3, wherein the surgery is LASEK.

[0159] Embodiment 6. The method of embodiment 3, wherein the surgery is PRK.

Embodiment 8. The method of embodiment 2, wherein the surgery is corneal transplantation.

Embodiment 9. The method of embodiment 8, wherein the corneal transplantation procedure includes penetrating keratoplasty, lamellar keratoplasty, anterior lamellar keratoplasty, deep anterior lamellar keratoplasty or endothelial keratoplasty.

Embodiment 10. The method of embodiment 2, wherein the surgery is pterygium excision.

Embodiment 11. The method of embodiment 2, wherein the infection gives rise to bacterial or viral keratitis.

Embodiment 12. The method of any one of embodiment 1 or 2, wherein the ocular fibrosis is stromal haze.

Embodiment 13. The method of any one of embodiment 1 or 2, wherein the ocular fibrosis is pterygia.

Embodiment 14. The method of embodiment 1, wherein the ocular fibrosis of the lens capsule is posterior capsule opacification incident to cataract surgery.

Embodiment 15. The method of embodiment 14, wherein the cataract surgery is phacoemulsification, manual small incision cataract surgery, extracapsular cataract extraction, or intracapsular cataract extraction.

Embodiment 16. The method of any one of the preceding embodiments wherein R is isopropyl.

Embodiment 17. A method for prevention and treatment of fibrotic invasion of the cornea, lens or lens capsule, the method including administering to a subject in need thereof an effective amount of the compound with structure of Formula (Γ)

\[
\text{Formula (Γ)}: \quad \begin{array}{c}
\text{OH} \\
\text{O} \\
\text{O} \\
\end{array}
\]

(A),

wherein:
R is hydrogen or \( \text{C}_1-\text{C}_6 \) alkyl.

[0171] Embodiment 18. The method of embodiment 17, wherein the effective amount of the compound with structure of Formula (\( \Gamma \)) inhibits the production or transport of inflammatory cells to the cornea.

[0172] Embodiment 19. The method of embodiment 17 or 18, wherein the fibrotic invasion of the cornea, lens or lens capsule includes myofibroblasts derived from bone marrow-derived fibrocysts or keratocyte-derived corneal fibroblasts.

[0173] Embodiment 20. The method of embodiment 19, wherein the effective amount of the compound with structure of Formula (\( \Gamma \)) is effective to block the transition of the myofibroblasts derived from bone marrow-derived fibrocysts or keratocyte-derived corneal fibroblasts in response to transforming growth factor beta (TGF\( \beta \)).


[0175] Embodiment 22. A pharmaceutical composition for topical administration, the composition including the compound with structure of Formula (\( \Gamma \)):

\[
\begin{align*}
\text{OH} & \quad \text{OH} & \quad \text{O} \quad R \\
\text{OC} & \quad \text{OC} & \quad \text{OC} & \quad \text{OC}
\end{align*}
\]

(\( \Gamma \)), in combination with a pharmaceutically acceptable excipient, wherein: R is hydrogen or \( \text{C}_1-\text{C}_6 \) alkyl.

[0176] Embodiment 23. The pharmaceutical composition of embodiment 22, the pharmaceutically acceptable excipient selected from one or more of polyoxyl lipid, fatty acid, and a polyalkoxylated alcohol.

[0177] Embodiment 24. The pharmaceutical composition of embodiment 23, wherein the pharmaceutically acceptable excipient is polyoxyl lipid or fatty acid.

[0178] Embodiment 25. The pharmaceutical composition of embodiment 24, wherein the pharmaceutically acceptable excipient is polyalkoxylated alcohol.
Embodiment 26. The pharmaceutical composition of any one of embodiments 23-25, further including nanomicelles.

Embodiment 27. The pharmaceutical composition of any one of embodiments 22-26 wherein R is isopropyl.
References


WHAT IS CLAIMED IS:

1. A method for the prevention and treatment of ocular fibrosis of the cornea, lens and lens capsule, said method comprising administering to a subject in need thereof an effective amount of the compound with structure of Formula (Fa):

   \[ \text{structure of Formula (Fa)} \]

   wherein:

   2. The method of claim 1, wherein said ocular fibrosis results from inflammatory cells or by proliferation of fibroblasts or fibroblast-like cells activated as a result of trauma, infection or surgery.

   3. The method of claim 2, wherein said surgery is laser-assisted in situ keratomileusis (LASIK), laser-assisted epithelial keratoplasty (LASEK) or photorefractive keratectomy (PRK).

   4. The method of claim 3, wherein said surgery is LASIK.

   5. The method of claim 3, wherein said surgery is LASEK.

   6. The method of claim 3, wherein said surgery is PRK.

   7. The method of claim 2, wherein said surgery involves removal of the natural lens and the implantation of an artificial intraocular lens.

   8. The method of claim 2, wherein said surgery is corneal transplantation.

   9. The method of claim 8, wherein said corneal transplantation procedure includes penetrating keratoplasty, lamellar keratoplasty, anterior lamellar keratoplasty, deep anterior lamellar keratoplasty or endothelial keratoplasty.
10. The method of claim 2, wherein said surgery is pterygium excision.

11. The method of claim 2, wherein said infection gives rise to bacterial or viral keratitis.

12. The method of any one of claim 1 or 2, wherein said ocular fibrosis is stromal haze.

13. The method of any one of claim 1 or 2, wherein said ocular fibrosis is pterygia.

14. The method of claim 1, wherein said ocular fibrosis of the lens capsule is posterior capsule opacification incident to cataract surgery.

15. The method of claim 14, wherein said cataract surgery is phacoemulsification, manual small incision cataract surgery, extracapsular cataract extraction, or intracapsular cataract extraction.

16. The method of any one of the preceding claims wherein R is isopropyl.

17. A method for prevention and treatment of fibrotic invasion of the cornea, lens or lens capsule, said method comprising administering to a subject in need thereof an effective amount of the compound with structure of Formula (Γ):

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{HO} & \quad \text{HO} \\
\text{O} & \quad \text{O} \\
\text{R} & \\
\end{align*}
\]

(Γ'),

wherein:

R is hydrogen or C<sub>6</sub> alkyl.

18. The method of claim 17, wherein said effective amount of the compound with structure of Formula (Γ) inhibits the production or transport of inflammatory cells to the cornea.

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19. The method of claim 17 or 18, wherein said fibrotic invasion of the
cornea, lens or lens capsule comprises myofibroblasts derived from bone marrow-derived
fibrocysts or keratocyte-derived corneal fibroblasts.

20. The method of claim 19, wherein said effective amount of the compound
with structure of Formula (Γ) is effective to block the transition of said myofibroblasts derived
from bone marrow-derived fibrocysts or keratocyte-derived corneal fibroblasts in response to
transforming growth factor beta (TGFb).

21. The method of any one of claims 17-20 wherein R is isopropyl.

22. A pharmaceutical composition for topical administration, said composition
comprising the compound with structure of Formula (Γ):

\[
\text{OH} \quad \text{OH} \quad \text{O} \quad R
\]

in combination with a pharmaceutically acceptable excipient,
wherein:
R is hydrogen or Ci-C₆ alkyl.

23. The pharmaceutical composition of claim 22, said pharmaceutically
acceptable excipient selected from one or more of polyoxyl lipid, fatty acid, and a
polyalkoxylated alcohol.

24. The pharmaceutical composition of claim 23, wherein said
pharmaceutically acceptable excipient is polyoxyl lipid or fatty acid.

25. The pharmaceutical composition of claim 24, wherein said
pharmaceutically acceptable excipient is polyalkoxylated alcohol.

26. The pharmaceutical composition of any one of claims 23-25, further
comprising nanomicelles.
27. The pharmaceutical composition of any one of claims 22-26 wherein R is isopropyl.
Figures 1A-1F.

Figures 2A-2C.
A. CLASSIFICATION OF SUBJECT MATTER
A61K 31/202(2006.01)i, A61K 31/20(2006.01)i, A61K 31/215(2006.01)i, A61P 27/02(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
A61K 31/202; A61P 27/02; C07C 69/734; C07C 57/00; A61K 47/34; C07C 69/732; A61K 9/107; C07C 59/42; A61K 31/215

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal), STN ( Registry, Caplus) & Keywords: ocular fibrosis, fibrotic invasion, cornea, eye, LASIK, LASEK, PRK, keratectomy, keratomileusis, keratooplasty, photo refractive, polyoxyl lipid, fatty acid

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>See abstract; paragraphs [0007], [0200]; examples 1-11; tables 1-9; claims 1-12.</td>
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<td>See abstract; figure V, page 4, 118-124; claims 1-14.</td>
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<td>WO 2009-051670 A2 (RESOLVYX PHARMACEUTICALS, INC. et al.) 23 April 2009</td>
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<td>TORRICELLI, ANDRE A. M. et al. Resolvin E1 analog RX-10045 0.1% reduces</td>
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<td>corneal stromal haze in rabbits when applied topically after PRK.</td>
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Further documents are listed in the continuation of Box C.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
24 November 2015 (24.11.2015)

Date of mailing of the international search report
24 November 2015 (24.11.2015)

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheonga-ro, Seo-gu, Daejeon, 35208, Republic of Korea
Facsimile No. +82-42-472-7140

Authorized officer
LEE, Jeong A
Telephone No. +82-42-481-8740

Form PCT/ISA/210 (second sheet) (January 2015)
Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos.: 1-21
   because they relate to subject matter not required to be searched by this Authority, namely:
   Claims 1-21 pertain to methods for treatment of the human body by surgery or therapy, and thus relate to a subject matter which this International Searching Authority is not required to search (PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv)).

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. **X** Claims Nos.: 16, 21, 27
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.
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