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(54) Title: THERAPEUTIC COMPOSITIONS FOR TREATMENT OF CORNEAL DISORDERS

(57) Abstract: The invention provides methods and compositions for minimizing, preventing, or treating damage to corneal nerves by administering to a subject with such damage or at risk of exposure to such damage a composition which blocks an activity of an IL-I cytokine and/or an IL-17 cytokine.

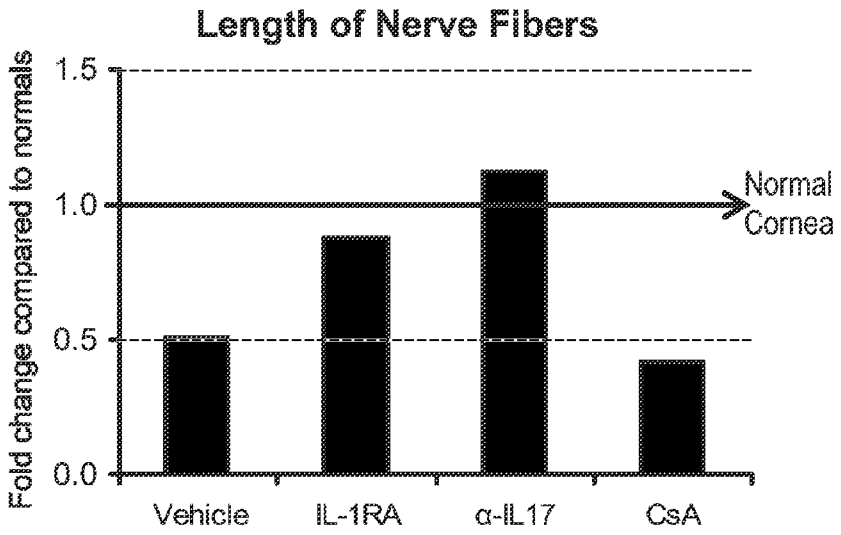


FIG. 8B

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THERAPEUTIC COMPOSITIONS FOR TREATMENT OF CORNEAL DISORDERS

RELATED APPLICATIONS

This application claims the benefit of U.S.S.N. 61/143,561, filed January 9, 2009, the contents of which are incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

This invention relates generally to the field of ophthalmology.

BACKGROUND OF THE INVENTION

Corneal epithelial damage can lead to chronic ocular surface disease. The mechanisms by which this occurs have not been elucidated, making the development of treatments that address the cause rather than the symptoms of chronic ocular surface disease difficult, if not impossible. As such, there has been a long-felt need in the art for the discovery of these mechanisms and for the development of compositions and methods of treatment.

SUMMARY OF THE INVENTION

The invention is based on the surprising discovery that IL-1 inhibition leads to corneal nerve regeneration. Moreover, the invention provides compositions and methods for treating neurotrophic dry eye disease by reducing damage to and regenerating corneal nerves. Nerve damage and increased immune activity within the cornea complete a vicious cycle of events, along with corneal epithelial damage, that would perpetuate itself and lead to chronic ocular surface disorders, but for the intervention of the treatments described herein. Neurotrophic dry (a neuropathic condition) eye is distinguished from other types of dry eye by a reduction or loss of corneal nerve tissue. For example, neurotrophic dry eye is characterized by a reduction or loss of at least about 10%, 25%, 50%, 75%, or more of corneal nerve tissue or corneal nerve fiber length compared to a normal condition.

The invention provides a method for protecting or treating corneal nerves in a subject in need thereof, including the steps of: (a) identifying a subject with corneal nerve damage or loss; and (b) locally administering to the cornea of the subject a composition that inhibits an activity of an inflammatory cytokine (e.g., IL-1or a combination of IL-1 and IL-17), thereby enhancing corneal nerve regeneration and reducing the development of abnormalities in

nerve morphology or density. Preferably, the subject has not been diagnosed as having meibomian gland dysfunction (MGD), *e.g.*, posterior blepharitis.

In one aspect of the above method, the subject is identified as having corneal nerve damage or loss that results from a congenital defect, disease, trauma, medical or surgical procedure. In another aspect of the above method, the subject is identified as having corneal nerve damage or loss that results from neurotrophic keratitis, herpes simplex, zoster keratitis, diabetes mellitus, trigeminal nerve damage, orbital or head surgery, head trauma, aneurysm, intracranial neurologic disease, keratorefractive procedures, photorefractive keratectomy (PRK), laser in situ keratomileusis (LASIK), congenital defect, ocular surface disease, dry eye syndrome, a non-ophthalmic disorder, a non-ophthalmic procedure, peripheral neuropathy, or diabetic neuropathy.

The invention further provides a method for minimizing or preventing damage or loss of corneal nerves in a subject in need thereof, including the steps of: (a) identifying the subject at risk of developing corneal nerve damage or loss; and (b) locally administering to the cornea of the subject a composition that inhibits an activity of an inflammatory interleukin-1 or interleukin-17 cytokine prior to development of nerve damage or loss, thereby decreasing nerve degeneration and reducing or preventing the development of abnormalities in nerve morphology or density.

In one aspect of the above method, the subject is identified as being at risk of exposure to corneal nerve damage or loss that could result from disease, trauma, or a medical procedure. In another aspect of the above method, the subject is identified as being at risk of exposure to corneal nerve damage or loss that could result from neurotrophic keratitis, herpes simplex keratitis, herpes zoster keratitis, diabetes mellitus, trigeminal nerve damage, orbital or head surgery, head trauma, aneurysm, intracranial neurologic disease, keratorefractive procedures, photorefractive keratectomy (PRK), laser in situ keratomileusis (LASIK), ocular surface disease, dry eye syndrome, a non-ophthalmic disorder, a non-ophthalmic procedure, peripheral neuropathy, or diabetic neuropathy.

In certain embodiments, the above methods further include the step of identifying a subject with a sign or symptom of corneal nerve damage or loss. For example, a sign of corneal nerve damage or loss is a decrease of corneal innervation or sensation, a reduction in the number of nerve fibers or bundles innervating the cornea, death of neurons innervating the cornea, a decrease or loss of neurotransmitter release, a decrease or loss of nerve growth factor release, abnormal tearing reflexes, abnormal blink reflexes, abnormal nerve

morphology, appearance of abnormal nerve sprouts, abnormal tortuosity, increased bead-like nerve formations, thinning of nerve fiber bundles, or thickening of nerve fiber bundles. For example, a symptom of corneal nerve damage or loss is abnormal tear production or dryness, abnormal blinking, and difficulty or loss of ability to focus, decreased or lost visual acuity, or decreased or lost corneal sensitivity.

In one aspect of the above methods, the activity includes binding of an inflammatory IL-1 cytokine to an IL-1 receptor. Compositions of the above methods that inhibit binding of an inflammatory IL-1 cytokine to an IL-1 receptor include an amino acid sequence of SEQ ID NO: 15 or SEQ ID NO: 16. Compositions optionally include inhibitors of IL-17 activity, *e.g.*, compounds that inhibit IL-17 binding to its receptor, or compounds that inhibit cytokines critical for generation of T helper-17/IL-17 response, such as inhibitors of IL-6 or inhibitors of IL-23. Preferably, the compositions do not include generic, broad spectrum immunosuppressive agents, such as cyclosporine A (CsA), as such non-specific suppressors of inflammation do not regenerate corneal nerves.

In each of the methods described herein, the composition is present in a concentration of 0.1-10 % (weight/volume or w/v). Alternatively, the composition is present in a concentration of 1.0 % (mg/ml), 1.5 % (mg/ml), 2.0 % (mg/ml), 2.5 % (mg/ml), 3.0 % (mg/ml), 3.5 % (mg/ml), 4.0 % (mg/ml), 4.5 % (mg/ml), 5.0 % (mg/ml), 5.5 % (mg/ml), 6.0 % (mg/ml), 6.5 % (mg/ml), 7.0 % (mg/ml), 7.5 % (mg/ml), 8.0 % (mg/ml), 8.5 % (mg/ml), 9.0 %(mg/ml), 9.5 % (mg/ml), 10.0 %(mg/ml), or any percentage point in between. In a preferred embodiment, the composition is present in a concentration of 2.5 % (mg/ml) or 5 % (mg/ml). For example, the composition is present in a concentration of 25 mg/ml or 50 mg/ml. Exemplary formulations contain an inhibitory composition present in a concentration of 2.5 % (25 mg/ml) or 5 %
(50 mg/ml).

The form of a composition of the above methods is a solid, a paste, an ointment, a gel, a liquid, an aerosol, a mist, a polymer, a film, an emulsion, or a suspension. The composition is administered topically. In a preferred embodiment, the above methods do not include systemic administration or substantial dissemination to non-ocular tissue. In certain embodiments of the above methods, the composition further includes a compound selected from the group consisting of a physiological acceptable salt, poloxamer analogs with carbopol, carbopol/HPMC, carbopol-methyl cellulose, a mucolytic agent, carboxymethylcellulose (CMC), hyaluronic acid, cyclodextrin, and petroleum. An exemplary

mucolytic agent is N-acetyl cysteine. In a preferred embodiment, the composition further includes carboxymethylcellulose (CMC).

Compositions of the above methods inhibit the transcription, transcript stability, translation, modification, localization, secretion, or function of a polynucleotide or polypeptide encoding an inflammatory interleukin-1 cytokine or an IL-1 receptor. In certain embodiments, a composition of the above methods includes a polynucleotide, a polypeptide, an antibody, or a small molecule. Alternatively, or in addition, a composition of the above methods includes a morpholino antisense oligonucleotide, microRNA (miRNA), short hairpin RNA (shRNA), or short interfering RNA (siRNA).

The invention provides a method for reducing or treating corneal lymphangiogenesis in a subject in need thereof, including the steps of: (a) identifying a subject with corneal lymphangiogenesis; and (b) locally administering to the cornea of the subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine, thereby inhibiting the ability of lymphatic vessels to expand within or invade corneal tissue and reducing or treating corneal lymphangiogenesis.

The invention provides a method for minimizing or preventing corneal lymphangiogenesis in a subject in need thereof, including the steps of: (a) identifying a subject at risk of developing lymphangiogenesis onset; and (b) locally administering to the cornea of the subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine prior to the development, thereby inhibiting the ability of lymphatic vessels to form or expand within, or to invade corneal tissue and minimizing or preventing corneal lymphangiogenesis.

The invention provides a method for reducing or treating the induction of immunity in a cornea of a subject in need thereof, including the steps of: (a) identifying a subject with an induction of immunity; and (b) locally administering to the cornea of the subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine, thereby inhibiting the ability of lymphatic vessels to expand within or to invade corneal tissue and reducing or treating the induction of immunity, wherein the lymphatic vessels permit the transport of immune cells between the corneal tissue and lymph nodes and the initiation of an immune response.

The invention provides a method for minimizing or preventing induction of immunity in a cornea of a subject in need thereof, including the steps of: (a) identifying the subject at risk of developing an immunity; and (b) locally administering to the cornea of the subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine prior to the

development, thereby inhibiting the ability of lymphatic vessels to expand within or to invade corneal tissue and minimizing or preventing induction of immunity, wherein the lymphatic vessels permit the transport of immune cells between the corneal tissue and lymph nodes and the initiation of an immune response.

The invention provides a method for reducing or treating an autoimmune condition affecting a corneal tissue of a subject in need thereof, including the steps of: (a) identifying a subject with the autoimmune condition; and (b) locally administering to the cornea of the subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine, thereby inhibiting the ability of lymphatic vessels to expand within or to invade corneal tissue and reducing or treating the autoimmune condition, wherein the lymphatic vessels permit the transport of immune cells between the corneal tissue and lymph nodes and the initiation of an immune response.

The invention provides a method for minimizing or preventing the development of an autoimmune condition affecting a corneal tissue of a subject in need thereof, including the steps of: (a) identifying a subject at risk of developing said autoimmune condition; and (b) locally administering to the cornea of the subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine prior to the development, thereby inhibiting the ability of lymphatic vessels to expand within or to invade corneal tissue and minimizing or preventing the development of the autoimmune condition, wherein the lymphatic vessels permit the transport of immune cells between said corneal tissue and lymph nodes and the initiation of an immune response.

In certain embodiments of the above methods, the subject has a dry-eye associated ocular surface disease. Alternatively, or in addition, the subject is at risk of developing a dry-eye associated ocular surface disease.

The ability of lymphatic vessels to expand within or to invade corneal tissue encompasses the potential or actual growth, expansion, elaboration, splitting, or remodeling of lymphatic vessels either within a corneal tissue or from a non-corneal tissue (such as the adjacent limbus) into corneal tissue. The phrase "lymphatic vessels permit the transport of immune cells" describes the unidirectional or bidirectional movement or deposition of an immune cell between a corneal tissue and a non-corneal tissue, preferably, a lymph node or other sites in the lymphoid compartment. Exemplary immune cells is include, but are not limited to, T cells, B cells, dendritic cells, macrophages, monocytes, and natural killer (NK) cells.

In one aspect of the above methods, the activity includes binding of an inflammatory

IL-1 cytokine to an IL-1 receptor. Compositions of the above methods that inhibit binding of an inflammatory IL-1 cytokine to an IL-1 receptor include an amino acid sequence of SEQ ID NO: 15 or SEQ ID NO: 16.

The form of a composition of the above methods is a solid, a paste, an ointment, a gel, a liquid, an aerosol, a mist, a polymer, a film, an emulsion, or a suspension. The composition is administered topically. In a preferred embodiment, the above methods do not include systemic administration or substantial dissemination to non-ocular tissue. In certain embodiments of the above methods, the composition further includes a compound selected from the group consisting of a physiological acceptable salt, poloxamer analogs with carbopol, carbopol/HPMC, carbopol-methyl cellulose, a mucolytic agent, carboxymethylcellulose (CMC), hyaluronic acid, cyclodextrin, and petroleum. An exemplary mucolytic agent is N-acetyl cysteine. In a preferred embodiment, the composition further includes carboxymethylcellulose (CMC).

Compositions of the above methods inhibit the transcription, transcript stability, translation, modification, localization, secretion, or function of a polynucleotide or polypeptide encoding an inflammatory interleukin-1 cytokine or an IL-1 receptor. In certain embodiments, a composition of the above methods includes a polynucleotide, a polypeptide, an antibody, or a small molecule. Alternatively, or in addition, a composition of the above methods includes a morpholino antisense oligonucleotide, microRNA (miRNA), short hairpin RNA (shRNA), or short interfering RNA (siRNA).

In certain embodiments of the above methods, the activity includes binding of an inflammatory IL-1 cytokine to an IL-1 receptor. Furthermore, compositions of the above methods that inhibit binding of an inflammatory IL-1 cytokine to an IL-1 receptor include the amino acid of SEQ ID NO: 15 or SEQ ID NO: 16. In certain embodiments, compositions of the above methods are present in a concentration of 0.1-10 % (mg/ml). Alternatively, the composition is present in a concentration of 1.0 % (mg/ml), 1.5 % (mg/ml), 2.0 % (mg/ml), 2.5 % (mg/ml), 3.0 % (mg/ml), 3.5 % (mg/ml), 4.0 % (mg/ml), 4.5 % (mg/ml), 5.0 % (mg/ml), 5.5 % (mg/ml), 6.0 % (mg/ml), 6.5 % (mg/ml), 7.0 % (mg/ml), 7.5 % (mg/ml), 8.0 % (mg/ml), 8.5 % (mg/ml), 9.0 %(mg/ml), 9.5 % (mg/ml), 10.0 %(mg/ml), or any percentage point in between. In a preferred embodiment, the composition is present in a concentration of 2.5 % (mg/ml) or 5 % (mg/ml). In another preferred embodiment, the composition is present in a concentration of 25 mg/ml or 50 mg/ml. In a further preferred embodiment, the composition is present in a concentration of 2.5 % (25 mg/ml) or 5 % (50 mg/ml).

In one aspect of the invention, the form of the compositions of the above methods is a solid, a paste, an ointment, a gel, a liquid, an aerosol, a mist, a polymer, a film, an emulsion, or a suspension.

Compositions of the above methods are administered topically. The above methods do not include systemic administration or substantial dissemination of the composition to non-ocular tissue.

In certain embodiments, compositions of the above methods further include a compound selected from the group consisting of a physiological acceptable salt, poloxamer analogs with carbopol, carbopol/HPMC, carbopol-methyl cellulose, N-acetyl cysteine, carboxymethylcellulose (CMC), hyaluronic acid, cyclodextrin, and petroleum. Preferably, the composition further includes N-acetyl cysteine or carboxymethylcellulose (CMC).

Alternatively, compositions of the above methods inhibit or enhance the transcription, transcript stability, translation, modification, localization, secretion, or function of a polynucleotide or polypeptide encoding the IL-1 receptor, type 2 (IL-1R2). IL-1R2 binds IL-1 and can inhibit the function of IL-1R1. Thus, in one embodiment, enhancement of IL-1R2 function provides another mechanism by which IL-1R1 activity is inhibited. In this same embodiment, inhibition of an antagonist of IL-1R2, specifically, IL-1Ra3, inhibits IL-1R1 function. Thus, the composition alone, or in combination with an enhancer of IL-1R2, inhibits the transcription, transcript stability, translation, modification, localization, secretion, or function of a polynucleotide or polypeptide encoding IL-1Ra3, SEQ ID NO: 22 or 23. Alternatively, in an embodiment wherein IL-1R2 receptor function augments the activity of IL-1R1, the composition contains one or more regions of a polynucleotide or polypeptide encoding IL-1Ra3 to augment IL-1R2 inhibition. Furthermore, the composition of this embodiment comprises the whole polynucleotide or polypeptide encoding IL-1Ra3.

Compositions of the methods of the invention include a polynucleotide, a polypeptide, an antibody, a compound, or a small molecule with means to inhibit the transcription, transcript stability, translation, modification, localization, secretion, or function of a polynucleotide or polypeptide encoding an accessory protein of an IL-1 Receptor. For example, this IL-1 receptor accessory protein is IL-1RAP, which directly binds IL-1 and IL-1R1, and is defined by the polynucleotide sequence of SEQ ID NO: 24 or 26 and the polypeptide sequence of
SEQ ID NO: 25 or 27. IL-1RAP belongs to a signaling complex that is required for signal transduction from IL-1R1. Thus, inhibition of IL-1RAP antagonizes IL-1R1 function.

In another embodiment, compositions of the methods of the invention include a polynucleotide, a polypeptide, an antibody, a compound, or a small molecule with means to inhibit the transcription, transcript stability, translation, modification, localization, secretion, or function of a polynucleotide or polypeptide encoding an associated kinase to an IL-1 receptor. For example, IL-1 receptor-associated kinase is IRAK1. IRAK1 is a downstream signaling effector that leads to transcriptional events associated with escalating inflammatory responses and is defined by the polynucleotide sequence of SEQ ID NO: 28, 30, or 32 and the polypeptide sequence of SEQ ID NO: 29, 31, or 33. Upon IL-1 receptor binding by IL-1, IRAK1 is recruited to the receptor complex, becomes hyperphosphorylated, and participates in the formation of a new protein complex consisting of hyperphosphorylated IRAK1 and TRAF6. The formation of this IRAK1/TRAF6 complex is a prerequisite for tumor necrosis factor (TNF) associated factor 6 (TRAF6)-mediated activation of nuclear factor-κB (NF-κB). Thus, the modification of the expression or function of any component of the above-delineated signaling cascade indicates a binding event between IL-1 to an IL-1 receptor.

Compositions of the methods of the invention include a polynucleotide, a polypeptide, an antibody, or a small molecule that binds or modifies the function of IL-1α, IL-1b, IL-1R1, IL-1R2, IL-1Ra3, IL-1RAP, IL-17, or IRAK1. Moreover the compositions include morpholino antisense oligonucleotides, microRNAs (miRNAs), short hairpin RNA (shRNA), or short interfering RNA (siRNA) to silence gene expression. Exemplary compounds to be adapted for topical administration include, but are not limited to, anakinra/Kineret® (recombinant human IL-1Ra, rhIL-1Ra, and SEQ ID NO: 15 and 16), IL-1R antisense oligomers (U.S. Patent No. 2005033694), IL-1Ra-like nucleic acid molecule (Amgen, U.S. Patent No. 2001041792), and polynucleotide encoding a soluble IL-1R accessory molecule (Human Genome Sciences, U.S. Issued Patent No. 6974682).

Compositions of the methods of the invention include microRNA molecules adapted for topical administration to the cornea in order to silence gene expression. Exemplary miRNAs that bind to human IL-1α include, but are not limited to, miR-30c (SEQ ID NO: 34), miR-30b (SEQ ID NO: 35), miR-30a-5p (SEQ ID NO: 36), and miR-24 (SEQ ID NO: 37). Exemplary miRNAs (and corresponding sequences) that bind to human IL-1R1 include, but are not limited to, miR-135b (SEQ ID NO: 38), miR-326 (SEQ ID NO: 39), miR-184 (SEQ ID NO: 40), miR-214 (SEQ ID NO: 41), miR-203 (SEQ ID NO: 42), miR-331 (SEQ ID NO: 43), and miR-205 (SEQ ID NO: 44).

Exemplary polypeptides to be adapted for topical administration to the cornea include, but are not limited to, anakinra/Kineret® (recombinant human IL-1Ra, rhIL-1Ra, and

SEQ ID NO: 15 and 16), AF12198 (binds human IL-1R1, Ac-FEWTPGWYQJYALPL-NH2 where J represents the unnatural amino acid, 2-azetidine-1-carboxylic acid, SEQ ID NO: 45), IL-1R and IL-1RAP peptide antagonists (U.S. Patent No. 20060094663), IL-1R accessory molecule polypeptides (U.S. Patent No. 20050171337), IL-1Ra peptides (U.S. Patent No. 2005105830), and IL-1Ra-related peptides (Amgen, U.S. Patent No. 2001042304).

Exemplary antibodies to be adapted for topical administration to the cornea include, but are not limited to, IL-1 TRAP (inline fusion double chain protein of IL1R-gp130 with hIgGFc, Regeneron, U.S. Issued Patent No. 6,927,044), anti-IL-1α (U.S. Patent No. 20030026806), anti-IL-1β (U.S. Patent No. 20030026806 and Yamasaki et al. Stroke. 1995; 26:676-681), and humanized monoclonal anti-IL-1R (Amgen, U.S. Patent No. 2004022718 and Roche, U.S. Patent No. 2005023872).

Small molecules are organic or inorganic. Exemplary organic small molecules include, but are not limited to, aliphatic hydrocarbons, alcohols, aldehydes, ketones, organic acids, esters, mono- and disaccharides, aromatic hydrocarbons, amino acids, and lipids. Exemplary inorganic small molecules comprise trace minerals, ions, free radicals, and metabolites. Alternatively, small molecule inhibitors can be synthetically engineered to consist of a fragment, or small portion, or a longer amino acid chain to fill a binding pocket of an enzyme. Typically small molecules are less than one kilodalton. An exemplary small molecule to be adapted for topical administration to the cornea is ZnPP (IL-1 blocker zinc protoporphyrin, naturally-occurring metabolite, Yamasaki et al. Stroke. 1995; 26:676-681).

Compositions of the methods of the invention include a polynucleotide, a polypeptide, an antibody, or a small molecule that binds or modifies the function of IL-1α, IL-1b, IL-1Ra, IL-1R1, IL-1R2, IL-1Ra3, IL-1RAP, IL-17, or IRAK1, administered topically with a pharmaceutically appropriate carrier. Delivery methods for polynucleotide compositions include, but are not limited to, liposomes, receptor-mediated delivery systems, naked DNA, and engineered viral vectors such as herpes viruses, retroviruses, adenoviruses and adeno-associated viruses, among others. Polynucleotide compositions are administered topically with a pharmaceutically acceptable liquid carrier, *e.g.*, a liquid carrier, which is aqueous or partly aqueous. Alternatively, polynucleotide sequences within the composition are associated with a liposome (*e.g.*, a cationic or anionic liposome).

A number of methods have been developed for delivering short DNA or RNA sequences into cells; *e.g.*, polynucleotide molecules can be contacted directly onto the tissue site, or modified polynucleotide molecules, designed to specifically target desired cell types

(*e.g.*, sequences linked to peptides or antibodies that specifically bind receptors or antigens expressed on the target cell surface).

A preferred approach uses a recombinant DNA construct in which the short polynucleotide sequence is placed under the control of a strong polymerase III or polymerase II promoter. The use of such a construct will result in the transcription of sufficient amounts of polynucleotide that will form complementary base pairs with the endogenous transcripts of nucleic acids of the invention and thereby prevent translation of endogenous mRNA transcripts. The invention encompasses the construction of a short polynucleotide using the complementary strand as a template. For example, a vector can be introduced *in vivo* such that it is taken up by a cell and directs the transcription of an interfering RNA or precursor to a double stranded RNA molecule. Alternatively, the template for the short polynucleotide transcript is placed under the transcriptional control of a cell-type specific promoter or other regulatory element. Thus, diffusion or absorption of a topically administered composition beyond the cornea does not cause deleterious or systemic side effects. The vector remains episomal or becomes chromosomally integrated, as long as it can be transcribed to produce the desired polynucleotide.

Vectors are constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in mammalian cells. Expression of the sequence encoding the short polynucleotide can be placed under the control of any promoter known in the art to act in mammalian, preferably human cells. Promoters are inducible or constitutive. Exemplary promoters include, but are not limited to: the SV40 early promoter region (Bernoist et al., Nature 290:304, 1981); the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., Cell, 22:787-797, 1988); the herpes thymidine kinase promoter (Wagner et al., Proc. Natl. Acad. Sci. USA, 78:1441, 1981); or the regulatory sequences of the metallothionein gene (Brinster et al., Nature, 296:39, 1988).

Polypeptide compositions are associated with liposomes alone or in combination with receptor-mediated delivery systems, to enable transport across the plasma membrane. Polypeptide compositions are soluble or membrane-bound. An exemplary receptor-mediated delivery system involves fusion of a low-density or very-low-density lipoprotein containing particle or vesicle to the low-density lipoprotein (LDL) receptor (LDLR) as observed with Hepatitis C Virus (HCV) infection and HCV-mediated drug delivery methods.

Compositions of the methods of the invention include one or more extracellular or intracellular antibodies, also called intrabodies, raised against one or more of the following:

IL-1α, IL-1b, IL-1Ra, IL-1R1, IL-1R2, IL-1Ra3, IL-1RAP, or IRAK1. Extracellular antibodies are topically administered with a pharmacologically appropriate aqueous or non-aqueous carrier. Sequences encoding intracellular antibodies are subcloned into a viral or mammalian expression vector, packed in a lipophilic device to facilitate transport across the plasma membrane, and topically administered to the cornea with a pharmacologically appropriate aqueous or non-aqueous carrier. Once inside the plasma membrane, host cell machinery transcribes, translates, and processes the intrabody code to generate an intracellular function-blocking antibody targeted against IL-1α, IL-1b, IL-1Ra, IL-1R1, IL-1R2, IL-1Ra3, IL-1RAP, or IRAK1. In the case of secreted molecules, intracellular antibodies prevent post-translational modification or secretion of the target protein. In the case of membrane-bound molecules, intracellular antibodies prevent intracellular signaling events upon receptor engagement by IL-1 cytokines.

In one preferred embodiment, methods of the invention includes a composition with means to inhibit the transcription, transcript stability, translation, modification, localization, secretion, or receptor binding of IL-1α, IL-1β, or a combination of both cytokines. In one embodiment, the composition comprises a polynucleotide capable of binding to a region of the IL-1α mRNA transcript, defined by SEQ ID NO: 1. In another embodiment, the composition comprises a polynucleotide capable of binding to a region of the IL-1β mRNA transcript, defined by SEQ ID NO: 3.

In another embodiment, the composition is capable of increasing the abundance of the naturally-occuring IL-1 Receptor antagonist (IL-1Ra). The composition comprises a polynucleotide, a polypeptide, an antibody, a compound, or a small molecule that binds to a region of the IL-1Ra gene, mRNA transcript defined by SEQ ID NO: 5, 7, 9, 11, or 13, a polypeptide isoform of IL-1Ra defined by SEQ ID NO: 6, 8, 10, 12, or 14, or a recombinant IL-1Ra protein defined by SEQ ID NO: 16. Alternatively, the composition contains mRNA transcripts or polypeptides encoding a region or the entirety of the IL-1Ra gene.

The composition includes an antagonist or inverse agonist of a receptor for IL-1α or IL-1β, specifically, IL-1R1. In this embodiment an antagonist is defined as a binding partner, or ligand, of an IL-1R that inhibits the function of an agonist, IL-1, or inverse agonist by blocking its binding to the receptor. An inverse agonist is defined as a molecule which binds to the same IL-1R binding-site as an agonist, for instance, IL-1, but exerts the opposite pharmacological effect. The composition contains a polynucleotide, a polypeptide, an antibody, a compound, or a small molecule that binds to a region of the IL-1R1 defined by

the polynucleotide and polypeptide sequences SEQ ID NO: 17-21. In an alternative embodiment, the composition includes a molecule with means to inhibit IL-1R transcription, transcript stability, translation, modification, localization, secretion, ligand binding, or association with an accessory protein of an IL-1R (IL-1RAP). IL-1RAP is defined by the polynucleotide sequence of SEQ ID NO: 24 or 26 and the amino acid sequence of SEQ ID NO: 25 or 27.

In another preferred embodiment, the composition includes a human recombinant IL-1R antagonist either in pure form, or as a component of a mixture. The human recombinant IL-1R antagonist is combined with balanced saline, carboxymethylcellulose (CMC), or hyaluronic acid (HA), or other vehicles prior to the composition contacting the cornea. Within these mixtures, the human recombinant IL-1R antagonist comprises at least 0.1%, 2.0%, 2.5%, 5%, or at most 10% of the total volume administered. Preferred aqueous formulations contain 2-2.5% of the purified antagonist. Purified is defined as the antagonist in the absence of unrelated polynucleotides, polypeptides, cellular organelles, or lipids. Purified is defines a degree of sterility that is safe for administration to a human subject, *e.g.*, lacking infectious or toxic agents.

All polynucleotides and polypeptides of the invention are purified and/or isolated. As used herein, an "isolated" or "purified" nucleic acid molecule, polynucleotide, polypeptide, or protein, is substantially free of other cellular material, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized. Purified compounds are at least 60% by weight (dry weight) the compound of interest. Preferably, the preparation is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight the compound of interest. Purity is measured by any appropriate standard method, for example, by column chromatography, polyacrylamide gel electrophoresis, or HPLC analysis.

Signs or symptoms of corneal damage or abnormal nerve morphology are detected, analyzed, examined, and evaluated using *in vivo* confocal microscopy (IVCM) of the central cornea or other imaging or diagnostic devices that allow for detection of corneal nerve damage. Exemplary devices for IVCM include, but are not limited to the Heidelberg Retina Tomograph 3 with the Rostock Cornea Module (HRT3/RCM)(Heidelberg Engineering GMBH) and the Confoscan 4 Confocal Microscope (Nidek, Inc.). In certain embodiments of the above methods, IVCM is used to detect, analyze, examine, and evaluate the form and number of nerve fibers in the various corneal layers, as well as to discriminate between parallel running, bifurcating,

branching, and interconnecting nerve fiber bundles. Alternatively or in addition, IVCM is used to detect, analyze, examine, and evaluate changes in the total number of nerves, changes in the length of nerves, nerve density, the presence or absence of abnormal nerve sprouts, the presence or absence of abnormal nerve fiber tortuosity, changes in number or morphology of bead-like nerve formations, and thinning versus thickening of nerve fiber bundles. In one aspect of the methods of the invention, IVCM is used to detect, analyze, examine, and evaluate nerve regeneration. Alternatively, or in addition, IVCM is used to detect, analyze, examine, and evaluate nerve degeneration. For instance, IVCM has been used to show an average of 6-8 corneal nerve bundles per image within the subbasal area of healthy individuals and nerve regeneration in patients who experienced nerve damage as a result of photoreceptive keratectomy.

The invention also provides a method for reducing corneal nerve damage and/or enhancing corneal nerve regeneration in a subject in need thereof, including the steps of: (a) identifying a subject with corneal nerve damage; and (b) locally administering to the cornea of the subject a composition that inhibits an activity of an inflammatory interleukin-17 cytokine, thereby enhancing corneal nerve regeneration, reducing the development of abnormalities in nerve morphology, and reducing corneal nerve damage.

The invention also provides a method for protecting or regenerating corneal nerves in a subject in need thereof, comprising the steps of: (a) identifying a subject with corneal nerve damage or loss; and (b) locally administering to the cornea of the subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine and a composition that inhibits an activity of an inflammatory interleukin-17 cytokine, thereby enhancing corneal nerve regeneration and reducing the development of abnormalities in nerve morphology or density. This combination therapy leads to a synergistic effect in regenerating corneal nerve tissue.

Publications, U.S. patents and applications, Genbank/NCBI accession numbers, and all other references cited herein, are herby incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A is a microphotograph that shows the extent of terminal nerve branching system at the level of basal epithelial cells in a normal cornea of a Balb/c mouse.

Figure 1B is a microphotograph of the terminal nerve processes following 7 days treatment with vehicle after epithelial debridement in a normal cornea of a Balb/c mouse, showing very minimal nerve regeneration activity at the level of the basal epithelial cells.

Figure 1C is a microphotograph of the regenerated terminal nerve processes following 7 days treatment with 2.5% topical IL-1Ra after epithelial debridement in a normal cornea of a Balb/c mouse, showing a significant number of regenerate nerves at the level of basal epithelial cells, bringing the density of these nerves close to that seen in normal corneas (Figure 1A).

Figure 2 is a series of *in vivo* confocal images (Confoscan 4; Nidek Technologies) of subbasal corneal nerve before (left) and after (right) a one-month treatment with IL-1Ra 2.5% in a dry eye patient, showing an increase of 25% in nerve density after the treatment compared to the baseline.

Figure 3 is a graph of the percent difference of corneal fluorescein staining observed in mouse models of dry eye treated with varying concentrations of IL-1Ra compared to untreated animals. As the graph shows, all concentrations of IL-1Ra (1%, 2.5%, and 5%) can decrease the corneal fluorescein staining score; however, the percent reduction of corneal fluorescein staining was modestly higher in the group that received topical IL-1Ra at a concentration of 5%.

Figure 4 is a graph of the percent difference of corneal fluorescein staining observed in mouse models of dry eye treated with varying formulations of IL-1Ra compared to untreated animals. As the graph shows, the percent reduction of corneal fluorescein staining was highest in the groups that received topical IL-1Ra 5% mixed with N-acetyl cysteine 10% and the group that received topical IL-1Ra 5% mixed with carboxymethyl cellulose 1%.

Figure 5 is a schematic representation of signaling pathways that are transduced from the IL-1RI and the downstream effectors involved in carrying these intracellular signals (drawing reproduced from BioCarta website).

Figure 6 is an in vivo confocal microscopic image (Confoscan 4; Nidek, Inc.) of subbasal nerve fibers in a healthy cornea of a 42-year-old male subject. Nerve bundles show a preferred orientation in the superior-inferior direction. Note the nerve fibers appear almost straight or slightly tortuous.

Figure 7 is an *in vivo* confocal microscopic image (Confoscan 4; Nidek, Inc.) of subbasal nerve fibers in the cornea of a 56-year-old female subject with herpes zoster ophthalmicus. Note the significant decrease in the number of nerve bundles compared to the normal cornea. This microphotograph also shows signs of other nerve abnormalities such as high tortuosity, increased bead-like nerve formations, and an abnormal branching pattern.

Figure 8A is a series of representative micrographs showing nerve fiber distribution in the central cornea of normal and dry eye disease (DED) mice. The white arrows show nerve

fiber loss (reduced nerve length) in the cornea of dry eye mice. Figure 8B is a bar diagram showing fold change (from normal cornea shown as horizontal solid arrow) in corneal nerve fiber length in DED mice treated topically with vehicle, IL-1Ra, anti-IL17-antibody, and cyclosporine-1 (CsA). Figure 8C is a bar diagram showing fold change (from normal cornea shown as horizontal solid arrow) in corneal nerve fiber tortuosity in DED mice treated with vehicle, IL-1Ra, anti-IL17-antibody, and cyclosporine-1 (CsA).

Figure 9A is a line graph demonstrating mean corneal fluorescein staining in 70 human patients with ocular surface inflammatory disorder and dry eyes treated with topical IL-1 receptor antagonist. Figure 9B is a bar graph demonstrating the percent change from baseline of corneal staining in the same patients treated with topical IL-1 receptor antagonist.

Figure 10A is a line graph demonstrating mean interpalpebral staining in 70 human patients with ocular surface inflammatory disorder and dry eyes treated with topical IL-1 receptor antagonist. Figure 10B is a bar graph demonstrating the percent change from baseline of interpalpebral staining in the same patients treated with topical IL-1 receptor antagonist.

Figure 11A is a line graph showing mean ocular surface disease index in 70 human patients with ocular surface inflammatory disorder and dry eyes treated with topical IL-1 receptor antagonist. Figure 11B is a bar graph showing the percent change from baseline of ocular surface disease index in the same patients treated with topical IL-1 receptor antagonist.

Figure 12 is a line graph demonstrating mean tear volume in 70 human patients with an ocular surface inflammatory disorder and dry eyes treated with topical IL-1 receptor antagonist.

Figure 13 is a series of photomicrographs depicting a corneal nerve regeneration in the human patients with ocular surface inflammatory disorder and dry eyes treated with topical IL-1 receptor antagonist or vehicle (lubricating eye drops).

DETAILED DESCRIPTION

IL-1, particularly IL-1β, has been reported to promote nerve regeneration. Earlier studies reported that IL-1β was upregulated or stimulated production of the neurotrophin, nerve growth factor (NGF) (Pons et al., 2002, Eur. Respir. J. 20:458-463; Akeda et al., 2007, Spine 32:635-642). For example, IL-1β inhibition using IL-1Ra was found to suppress a neurotrophin response in injured brain tissue. An increase in nerve growth factor (NGF) was found to be directly mediated through IL-1β and blocking IL-1β with IL-1Ra led to

suppression of the NGF-mediated reparative response (DeKosky et al., 1996, Ann. Neurol. 39:123-127). The data reported herein indicate that IL-1 blockade stimulates corneal nerve regeneration, an unexpected and surprising finding that contradicts these earlier reports.

IL-1 blockade was used to treat patients characterized by complaints of chronic ocular irritation and discomfort. Using an animal model and clinical studies, compositions and methods of the invention demonstrate that corneal nerves are protected and indeed regenerated by inhibiting the action of IL-1. Specifically, IL-1 blockade through topical administration of IL-1 Receptor antagonist (IL-1Ra), which acts as an antagonist to IL-1, protects corneal nerves, enhances corneal nerve regeneration, and reduces the abnormalities in subbasal nerve morphology.

Exemplary abnormalities in subbasal nerve morphology include, but are not limited to the presence of abnormal nerve sprouts, abnormal tortuosity, increased bead-like formation, and thinning or thickening of nerve fiber bundles. Thus, IL-1 inhibitors are protective in neuropathic conditions such as herpes simplex or zoster keratitis, diabetes mellitus, dry eye, exposure keratopathy, trigeminal nerve damage associated with orbital or head surgery, head trauma, aneurysms, or intracranial neurologic disease, and corneal nerve damage associated with keratorefractive procedures such as PRK and LASIK.

Corneal nerves are characterized by unique anatomical location, structural features, and functions, compared to other nerves, *e.g.*, the cornea is an avascular location and has unmyelinated nerve endings sensitive to touch, temperature and chemicals. A touch of the cornea or other stimulus causes an involuntary reflex to close the eyelid.

Although some earlier reports describe interleukins and nervous system disorders, the corneal neuroprotective effect of IL-1 blockade is has not been observed prior to the invention described herein. US6,623,736 refers to interleukins and retinal and optic nerve disorders, but not the cornea or ocular surface. Optic neuritis, macular degeneration, retinitis pigmentosa, and diabetic retinopathy have entirely different pathophysiologic mechanisms, natural histories, epidemiologies, treatments and clinical presentations, as compared to the corneal and ocular surface disorders discussed herein. US20030083301 refers to treatment of spinal cord injuries. The spinal cord, part of the central nervous system, has a physiology, pathobiology, and anatomy distinct from the peripheral nerves of the cornea. There is no mention of any ocular disorders in US20030083301. US20090136453 and US20080242634 refer to methods of administering an IL-1 antagonist for treating pain, but do not describe corneal nerves or degeneration thereof. The invention described herein relates to damage of

corneal nerves that can occur without surgical trauma, such as natural disease processes including chronic ocular surface disorders.

Prior to the invention, scientific literature reported that IL-1 induces expression of nerve growth factor (NGF), which is involved in nerve regeneration and survival. For example, Temporin (Temporin *et al.*, 2008 Neurosci Lett., 440(2): 130-3) reports that IL-1 promotes sensory nerve regeneration. Ryoke (Ryoke *et al.*, 2000 Biochem Biophys Res Commun., 267(3): 715-8) reports that IL-1 expression is associated with *in vivo* nerve regeneration. Guenard (Guenard *et al.*, 1991 J Neurosci Res., 29(3): 396-400) reports that the IL-1 antagonist, IL-1 receptor antagonist (IL-1Ra), impedes peripheral nerve regeneration. Due to the unique nature of corneal nerves, IL-1 inhibition (and the combination of IL-1 and IL-17 inhibition) has a completely different effect in accordance with the invention compared to the earlier reports.

Corneal Structure

The cornea is the transparent front part of the eye that covers the iris, pupil, and anterior chamber. Together with the lens, the cornea refracts light, and as a result helps the eye to focus, accounting for approximately two-thirds of the eye's total optical power. The cornea has unmyelinated nerve endings sensitive to touch, temperature and chemicals; a touch of the cornea causes an involuntary reflex to close the eyelid.

Because transparency is of prime importance the cornea does not have blood vessels; it receives nutrients via diffusion from the tear fluid at the outside and the aqueous humor at the inside and also from neurotrophins supplied by nerve fibers that innervate it. In humans, the cornea has a diameter of about 11.5 mm and a thickness of 0.5–0.6 mm in the center and 0.6–0.8 mm at the periphery. Transparency, avascularity, the presence of highly immature resident immune cells, and immunologic privilege makes the cornea a unique tissue. Immune privilege is meant to describe certain sites in the body that are able to tolerate the introduction of an antigen without eliciting an inflammatory immune response. The cornea has no blood supply, but rather, the cornea it gets oxygen directly through the air and the tears that bathe it.

The human cornea, like that of other primates, has five layers. From the anterior to posterior they are the corneal epithelium, Bowman's layer, the corneal stroma, Descemet's membrane, and the corneal endothelium. The corneal epithelium is a thin epithelial multicellular tissue layer, stratified squamous epithelium, of continuously regenerating cells, kept moist with tears. Irregularity or edema of the corneal epithelium disrupts the smoothness of the air-tear film interface, the most significant component of the total refractive power of the eye, thereby reducing visual acuity. Bowman's layer, also known as

the anterior limiting membrane, is a condensed layer of irregularly-arranged collagen, about 8-14 microns thick, that protects the corneal stroma. The corneal stroma, also known as the substantia propria, is a thick and transparent middle layer, consisting of regularly-arranged collagen fibers along with sparsely populated keratocytes. The corneal stroma consists of approximately 200 layers of type I collagen fibrils. Ninety percent of the corneal thickness is composed of the stroma. Descemet's membrane, also known as the posterior limiting membrane, is a thin and acellular layer that serves as the modified basement membrane of the corneal endothelium. The corneal endothelium is a simple squamous or low cuboidal monolayer of mitochondria-rich cells responsible for regulating fluid and solute transport between the aqueous and corneal stromal compartments. The corneal endothelium is bathed by aqueous humour, not by blood or lymph, and has a very different origin, function, and appearance from vascular endothelia. Unlike the corneal epithelium, the cells of the endothelium do not regenerate. Instead, corneal endothelial cells expand or spread to compensate for dead cells which reduces the overall cell density of the endothelium and impacts fluid regulation.

The cornea is one of the most sensitive tissues of the body, it is densely innervated with sensory nerve fibers via the ophthalmic division of the trigeminal nerve by way of 70 - 80 long and short ciliary nerves. Nerves enter the cornea via three levels, scleral, episcleral and conjunctival. Most of the bundles subdivide and form a network in the stroma, from which fibers supply different regions of the cornea. Three exemplary networks are midstromal, subepithelial/Bowman's layer, and epithelium. Corneal nerves of the subepithelial layer converge and terminate near the apex of the cornea.

Corneal Innervation

The cornea is one of the most densely innervated tissues in the body and is abundantly supplied by different types of nerve fibers. Rabbit studies have revealed that the nerve density of the corneal epithelium is about 300-600 times as much as that of skin and 20-40 times that of the dental pulp. It is estimated that there are approximately 7000 sensory receptors per mm^2 in the human corneal epithelium, implying that injuries to individual epithelial cells may be adequate to give a pain perception (Müller *et al.*, Exp Eye Res 2003;76:521-42).

Most corneal nerve fibers are sensory in origin and are derived from the ophthalmic branch of the trigeminal nerve. Nerve bundles enter the peripheral mid-stromal cornea in a radial fashion parallel to the corneal surface. Soon after entering the cornea, the main stromal bundles branch repeatedly and dichotomously into smaller fascicles that ascended into

progressively more superficial layers of the stroma. Eventually, the stromal nerve fibers turn abruptly 90°, penetrate Bowman's layer and proceed towards the corneal surface. After penetrating Bowman's layer, bundles divide and run parallel to the corneal surface between Bowman's layer and the basal epithelium, forming the subbasal nerve plexus. The density and number of nerves in the subbasal epithelial nerve plexus are significantly greater than the density and number of nerves in the remaining corneal layers. Subbasal fibers subsequently form branches that turn upward and enter the corneal epithelium between the basal cells to reach the wing cells, where they terminate (Müller *et al.*, Invest Ophthalmol Vis Sci 1996;37:476-88).

Corneal nerve fibers mediate not only sensation but also exert critical trophic influences on the corneal epithelium and play a vital role to the preservation of a healthy ocular surface. Corneal sensation is a key mechanism in preventing injury through the blink reflex and reflex tearing. Neuropathy, *e.g.*, degeneration of corneal nerves, leads to changes in sensation. Patients diagnosed with neuropathy of the corneal nerve experience diminished sensation and/or increased pain (hyperalgesia), characterized by chronic discomfort and irritation. Since lacrimation is regulated by the corneal nerves, corneal neuropathy (loss or damaged corneal nerve tissue or decreased length of corneal nerve fibers) leads to tear deficiency. Thus, the methods are useful to reduce the symptoms of tear-deficient dry eye.

Dysfunction of corneal innervation and related neuropathic pathology produces a degenerative condition known clinically as "neurotrophic keratitis", which therefore renders the corneal surface vulnerable to occult injury and delayed healing of established corneal epithelial injuries. Most clinical cases of neurotrophic keratitis are caused by herpes simplex or zoster keratitis, diabetes mellitus, or by trigeminal nerve damage associated with orbital or head surgery, head trauma, aneurysms, or intracranial neurologic disease. Absent or reduced corneal sensation may be congenital in origin. Keratorefractive procedures such as photorefractive keratectomy (PRK) and laser *in situ* keratomileusis (LASIK) can sever stromal and subbasal corneal nerves plexus and produce a transient mild to severe neuropathologic condition, or neurotrophic dry eye. This form of "neurotrophic dry eye", characterized by nerve loss and associated dryness, is also seen in non-surgical conditions such as severe forms of dry eye that develop in subjects.

Intact corneal innervation is also mandatory for tearing reflexes. Under normal physiological conditions, sensory nerves in the cornea transmit an afferent stimulation signal to the brain stem and then, after a series of interneurons, the efferent signal is transmitted to the lacrimal gland through the parasympathetic and sympathetic nerves that innervate the

gland and drive tear production and secretion (Dartt, DA Ocul Surf 2004;2:76-91). Damage to this neural circuit interrupts the normal regulation of lacrimal gland secretion and causes dry eye disease. A reduction in neural drive from the cornea favors the occurrence of dry eye-associated ocular surface disease in two ways; first, by decreasing reflex-induced lacrimal secretion and by reducing the blink rate and, consequently, increasing evaporative loss; second, by decreasing the trophic factors to the epithelial layer. Damage to the sensory nerves in the ocular surface, particularly the cornea, as a consequence of refractive surgery and normal aging, prevents the normal reflex arc to the lacrimal gland and can result in decreased tear secretion and dry eye syndromes. Evidence for this mechanism comes from the clinical observation that dry eye syndrome frequently occurs after corneal refractive surgery (*e.g.*, surgery in which the nerve is transected). Clinical studies confirmed that tear production and secretion are reduced after LASIK surgery (Battat *et al.*, Ophthalmology 2001;108:1230-5). Interestingly, hyposecretion of tears in dry eye may lead to pathologic alterations in corneal nerves and a decline in corneal sensitivity which subsequently perpetuate the dry eye state (Xu *et al.*, Cornea 1996;15:235-9). Dry eye is further described in PCT/US2008/009776, which is incorporated herein by reference.

Patients with only meibomian gland disease (MGD) or posterior blepharitis are generally not characterized as having clinical neuropathy (clinically significant corneal nerve damage), and hence do not have "neurotrophic" dry eye.

Corneal Pathology

Ocular diseases that affect the corneal epithelium such as dry eye, exposure keratopathy, and other ocular surface diseases cause corneal nerve degeneration. On the other hand, normal neural drive is an essential requirement for corneal epithelium to heal and maintain its homeostasis. Therefore, corneal nerve alterations, either as a primary reason (refractive surgery) or just as the outcome of dryness and other corneal epithelial or ocular surface diseases, have crucial effects on the homeostasis of corneal epithelium, thus neatly contributing to the increase of the vicious cycle of epithelial disease and nerve damage.

Interleukin-1 (IL-1)

The IL-1 family is a group of cytokines that function as major mediators of inflammation and immune response (Dinarello, C.A. 1996. Blood. 15:2095-2147). This family is composed of three forms: two proinflammatory forms, IL-1α and IL-1ß, each having a precursor form, and an anti-inflammatory form, IL-1 receptor antagonist (IL-1Ra).

The proinflammatory cytokine IL-1 plays an important role in inflammation and immunity by increasing chemokine production, adhesion factors, macrophage infiltration and activity, and lymphocyte proliferation. IL-1 has been implicated in the pathogenesis of human inflammatory diseases, such as rheumatoid arthritis, septic shock, and periodontitis (Jiang, Y. et al. 2000. Arthritis Rheum. 43:1001-1009; Okusawa, S. et al. 1988. J Clin Invest. 81: 1162-1172; McDevitt, M.J. et al. 2000. J. Periodontol. 71:156-163).

The compositions and methods described herein inhibit the activity of human IL-1α and/or IL-1β, as defined by the ability to induce signal transduction or initiate/activate a downstream signaling cascade from an IL-1 receptor. Compositions that contain an inhibitor of human IL-1α or IL-1β function antagonize the activity of an IL-1 receptor. The composition comprises a polynucleotide, a polypeptide, an antibody, a compound, or a small molecule with means to inhibit the transcription, transcript stability, translation, modification, localization, secretion, or function of a polynucleotide or polypeptide encoding human IL-1α or IL-1β. Moreover, the inhibitory polynucleotide or polypeptide composition binds to one or more region(s) of IL-1α or IL-1β comprised by SEQ ID NO: 1 and SEQ ID NO: 2 (IL-1α) or SEQ ID NO: 3 and SEQ ID NO: 4 (IL-1β). The inhibitory polynucleotide or polypeptide composition binds to one or more fragments of IL-1α or IL-1β comprised by SEQ ID NO: 1 and

SEQ ID NO: 2 (IL-1α) or SEQ ID NO: 3 and SEQ ID NO: 4 (IL-1β).

A fragment, in the case of these sequences and all others provided herein, is defined as a part of the whole that is less than the whole. Moreover, a fragment ranges in size from a single nucleotide or amino acid within a polynucleotide or polypeptide sequence to one fewer nucleotide or amino acid than the entire polynucleotide or polypeptide sequence. Finally, a fragment is defined as any portion of a complete polynucleotide or polypeptide sequence that is intermediate between the extremes defined above.

Human IL-1α is encoded by the following mRNA sequence (NCBI Accession No. NM_000575 and SEQ ID NO: 1): (For all mRNA transcripts incorporated into the present application, the initiator methionine, encoded by the codon "atg," is bolded and capitalized to delineate the start of the coding region.)

accaggcaacaccattgaaggctcatatgtaaaaatccatgccttcctttctcccaatctccattccc
aaacttagccactggcttctggctgaggccttacgcatacctcccggggcttgcacacaccttcttct
acagaagacacaccttgggcatatcctacagaagaccaggcttctctctggtccttggtagagggcta
ctttactgtaacagggccagggtggagagttctctcctgaagctccatcccctctataggaaatgtgt
tgacaatattcagaagagtaagaggatcaagacttctttgtgctcaaataccactgttctcttctcta
ccctgccctaaccaggagcttgtcaccccaaactctgaggtgatttatgccttaatcaagcaaacttc
cctcttcagaaaagatggctcattttccctcaaaagttgccaggagctgccaagtattctgccaattc

accctggagcacaatcaacaaattcagccagaacacaactacagctactattagaactattattatta
ataaattcctctccaaatctagccccttgacttcggatttcacgatttctcccttcctcctagaaact
tgataagtttcccgcgcttccctttttctaagactacatgtttgtcatcttataaagcaaaggggtga
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aagtcaag**ATG**gccaaagttccagacatgtttgaagacctgaagaactgttacagtgaaaatgaagaa
gacagttcctccattgatcatctgtctctgaatcagaaatccttctatcatgtaagctatggcccact
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taggtcagcacctttagcttcctgagcaatgtgaaatacaactttatgaggatcatcaaatacgaat
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ttacataatctggatgaagcagtgaaatttgacatgggtgcttataagtcatcaaaggatgatgctaa
aattaccgtgattctaagaatctcaaaaactcaattgtatgtgactgcccaagatgaagaccaaccag
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gcaagactactgggtgtgcttggcaggggggccaccctctatcactgactttcagatactggaaaacc
aggcgtaggtctggagtctcacttgtctcacttgtgcagtgttgacagttcatatgtaccatgtacat
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gccttctacttttaagttgctgatgaactcttaatcaaatagcataagtttctgggacctcagtttta
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aacccccttcatcctctgagtgtgaccaggcatcctccacaatagcagacagtgttttctgggataagt
aagtttgatttcattaatacagggcattttggtccaagttgtgcttatcccatagccaggaaactctg
cattctagtacttgggagacctgtaatcatataataaatgtacattaattaccttgagccagtaattg
gtccgatctttgactcttttgccattaaacttacctgggcattcttgtttcaattccacctgcaatca
agtcctacaagctaaaattagatgaactcaactttgacaaccatgagaccactgttatcaaaactttc
ttttctggaatgtaatcaatgtttcttctaggttctaaaaattgtgatcagaccataatgttacatta
ttatcaacaatagtgattgatagagtgttatcagtcataactaaataaagcttgcaacaaaattctct
gacaaaaaaaaaaaaaaaa.

Human IL-1α is encoded by the following amino acid sequence (NCBI Accession No.

NM_000575 and SEQ ID NO: 2):

MAKVPDMFEDLKNCYSENEEDSSSIDHLSLNQKSFYHVSYGPLHDSEEEIIKPRSAPFS
FLSNVKYNFMRIIKYEFILNDALNQSIIRANDQYLTAAALHNLDEAVKFDMGAYKSS
KDDAKITVILRISKTQLYVTAQDEDQPVLLKEMPEIPKTITGSETNLLFFWETHGTKN
YFTSVAHPNLFIATKQDYWVCLAGGPPSITDFQILENQA.

Human IL-1β is encoded by the following mRNA sequence (NCBI Accession No.

NM_000576 and SEQ ID NO: 3):

accaaacctcttcgaggcacaaggcacaacaggctgctctgggattctcttcagccaatcttcattgc
tcaagtgtctgaagcagcc**ATG**gcagaagtacctgagctcgccagtgaaatgatggcttattacagtg
gcaatgaggatgacttgttctttgaagctgatggccctaaacagatgaagtgctccttccaggacctg
gacctctgccctctggatggcggcatccagctacgaatctccgaccaccactacagcaagggcttcag
gcaggccgcgtcagttgttgtggccatggacaagctgaggaagatgctggttccctgcccacagacct
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tgggataacgaggcttatgtgcacgatgcacctgtacgatcactgaactgcacgctccgggactcaca
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agcaacaagtggtgttctccatgtcctttgtacaaggagaagaaagtaatgacaaaatacctgtggcc
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aaatcaataacaagctggaatttgagtctgcccagttccccaactggtacatcagcacctctcaagca
gaaaacatgcccgtcttcctgggagggaccaaaggcggccaggatataactgacttcaccatgcaatt
tgtgtcttcctaaagagagctgtacccagagagtcctgtgctgaatgtggactcaatccctagggctg
gcagaaagggaacagaaaggtttttgagtacggctatagcctggactttcctgttgtctacaccaatg
cccaactgcctgccttagggtagtgctaagaggatctcctgtccatcagccaggacagtcagctctct
cctttcagggccaatccccagccctttgttgagccaggcctctctcacctctcctactcacttaaag
cccgcctgacagaaaccacggccacatttggttctaagaaaccctctgtcattcgctcccacattctg
atgagcaaccgcttccctatttatttatttatttgtttgtttgttttattcattggtctaatttattc
aaaggggcaagaagtagcagtgtctgtaaaagagcctagtttttaatagctatggaatcaattcaat
ttggactggtgtgctctctttaaatcaagtcctttaattaagactgaaaatatataagctcagattat
ttaaatgggaatatttataaatgagcaaatatcatactgttcaatggttctgaaataaacttcactga
ag.

Human IL-1β is encoded by the following amino acid sequence (NCBI Accession No. NM_000576 and SEQ ID NO: 4):

MAEVPELASEMMAYYSGNEDDLFFEADGPKQMKCSFQDLDLCPLDGGIQLRISDHH
YSKGFRQAASVVVAMDKLRKMLVPCPQTFQENDLSTFFPFIFEEEPIFFDTWDNEAY
VHDAPVRSLNCTLRDSQQKSLVMSGPYELKALHLQGQDMEQQVVFSMSFVQGEES
NDKIPVALGLKEKNLYLSCVLKDDKPTLQLESVDPKNYPKKKMEKRFVFNKIEINNK
LEFESAQFPNWYISTSQAENMPVFLGGTKGGQDITDFTMQFVSS.

Interleukin-1 Receptor (type 1) antagonist (IL-1Ra):

IL-1Ra is an endogenous receptor antagonist which is primarily produced by activated monocytes and tissue macrophages, inhibits the activities of the proinflammatory forms of IL-1 by competitively binding to IL-1 receptor. (Gabay, C. et al. 1997. 159: 5905-5913). IL-1Ra is an inducible gene that is typically upregulated in inflammatory conditions (Arend, W.P. 1993. Adv Immunol. 54: 167-223).

In the present invention, compositions comprise one or more regions of IL-1Ra transcripts 1, 2, 3, or 4, intacellular IL-1Ra (icIL-1Ra), or their corresponding polypeptide isoforms. Alternatively, compositions comprise the entirety of IL-1Ra transcripts 1, 2, 3, or 4, intacellular IL-1Ra (icIL-1Ra), or their corresponding polypeptide isoforms. Compositions comprising any form of human IL-1Ra, or fragments thereof, inhibit the function of IL-1R1. These polynucleotides and polypeptides are defined by the following sequences.

Human IL-1Ra, transcript 1, is encoded by the following mRNA sequence (NCBI Accession No. NM_173842 and SEQ ID NO: 5):

atttctttataaaccacaactctgggcccgcaatggcagtccactgccttgctgcagtcacaga**ATG**g
aaatctgcagaggcctccgcagtcacctaatcactctcctcctcttcctgttccattcagagacgatc
tgccgaccctctgggagaaaatccagcaagatgcaagccttcagaatctgggatgttaaccagaagac
cttctatctgaggaacaaccaactagttgctggatacttgcaaggaccaaatgtcaatttagaagaaa

agatagatgtggtacccattgagcctcatgctctgttcttgggaatccatggagggaagatgtgcctg
tcctgtgtcaagtctggtgatgagaccagactccagctggaggcagttaacatcactgacctgagcga
gaacagaaagcaggacaagcgcttcgccttcatccgctcagacagcggccccaccaccagttttgagt
ctgccgcctgccccggttggttcctctgcacagcgatggaagctgaccagcccgtcagcctcaccaat
atgcctgacgaaggcgtcatggtcaccaaattctacttccaggaggacgagtagtactgcccaggcct
gcctgttcccattcttgcatggcaaggactgcagggactgccagtccccctgccccagggctcccggc
tatgggggcactgaggaccagccattgaggggtggaccctcagaaggcgtcacaagaacctggtcaca
ggactctgcctcctcttcaactgaccagcctccatgctgcctccagaatggtctttctaatgtgtgaa
tcagagcacagcagcccctgcacaaagcccttccatgtcgcctctgcattcaggatcaaaccccgacc
acctgcccaacctgctctcctcttgccactgcctcttcctccctcattccaccttcccatgccctgga
tccatcaggccacttgatgaccccaaccaagtggctcccacaccctgttttacaaaaaagaaaagac
cagtccatgagggaggtttttaagggtttgtggaaaatgaaaattaggatttcatgatttttttttct
cagtccccgtgaaggagagcccttcatttggagattatgttctttcggggagaggctgaggacttaaa
atattcctgcatttgtgaaatgatggtgaaagtaagtggtagcttttcccttcttttttcttcttttt
tgtgatgtcccaacttgtaaaaattaaaagttatggtactatgttagccccataatttttttttcct
tttaaaacacttccataatctggactcctctgtccaggcactgctgcccagcctccaagctccatctc
cactccagatttttacagctgcctgcagtactttacctcctatcagaagtttctcagctcccaaggc
tctgagcaaatgtggctcctgggggttctttcttcctctgctgaaggaataaattgctccttgacatt
gtagagcttctggcacttggagacttgtatgaaagatggctgtgcctctgcctgtctcccccaccggg
ctgggagctctgcagagcaggaaacatgactcgtatatgtctcaggtccctgcagggccaagcaccta
gcctcgctcttggcaggtactcagcgaatgaatgctgtatatgttgggtgcaaagttccctacttcct
gtgacttcagctctgttttacaataaaatcttgaaaatgcctaaaaaaaaaaaaaaaaaa.

Human IL-1Ra, transcript 1, is encoded by the following amino acid sequence (NCBI Accession No. NM_173842 and SEQ ID NO: 6):

MEICRGLRSHLITLLLFLFHSETICRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAG
YLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSEN
RKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYF
QEDE.

Human IL-1Ra, transcript 2, is encoded by the following mRNA sequence (NCBI Accession No. NM_173841 and SEQ ID NO: 7):

gggcagctccaccctgggagggactgtggcccaggtactgcccgggtgctactttatgggcagcagct
cagttgagttagagtctggaagacctcagaagacctcctgtcctatgaggccctcccc**ATG**gctttag
ctgacttgtatgaagaaggaggtggaggaggaggagaaggtgaagacaatgctgactcaaaggagacg
atctgccgaccctctgggagaaaatccagcaagatgcaagccttcagaatctgggatgttaaccagaa
gaccttctatctgaggaacaaccaactagttgctggatacttgcaaggaccaaatgtcaatttagaag
aaaagatagatgtggtacccattgagcctcatgctctgttcttgggaatccatggagggaagatgtgc
ctgtcctgtgtcaagtctggtgatgagaccagactccagctggaggcagttaacatcactgacctgag
cgagaacagaaagcaggacaagcgcttcgccttcatccgctcagacagcggccccaccaccagttttg
agtctgccgcctgccccggttggttcctctgcacagcgatggaagctgaccagcccgtcagcctcacc
aatatgcctgacgaaggcgtcatggtcaccaaattctacttccaggaggacgagtagtactgcccagg
cctgcctgttcccattcttgcatggcaaggactgcagggactgccagtccccctgccccagggctccc
ggctatgggggcactgaggaccagccattgaggggtggaccctcagaaggcgtcacaagaacctggtc
acaggactctgcctcctcttcaactgaccagcctccatgctgcctccagaatggtctttctaatgtgt
gaatcagagcacagcagcccctgcacaaagcccttccatgtcgcctctgcattcaggatcaaaccccg
accacctgcccaacctgctctcctcttgccactgcctcttcctccctcattccaccttcccatgccct
ggatccatcaggccacttgatgaccccaaccaagtggctcccacaccctgttttacaaaaaagaaaa
gaccagtccatgagggaggttttaagggtttgtggaaaatgaaaattaggatttcatgatttttttt
tttcagtccccgtgaaggagagcccttcatttggagattatgttctttcggggagaggctgaggactt
aaaatattcctgcatttgtgaaatgatggtgaaagtaagtggtagcttttcccttcttttttcttcttt
ttttgtgatgtcccaacttgtaaaaattaaaagttatggtactatgttagccccataatttttttttt
ccttttaaaacacttccataatctggactcctctgtccaggcactgctgcccagcctccaagctccat

ctccactccagatttttacagctgcctgcagtactttacctcctatcagaagtttctcagctcccaa
ggctctgagcaaatgtggctcctgggggttctttcttcctctgctgaaggaataaattgctccttgac
attgtagagcttctggcacttggagacttgtatgaaagatggctgtgcctctgcctgtctccccacc
gggctgggagctctgcagagcaggaaacatgactcgtatatgtctcaggtccctgcagggccaagcac
ctagcctcgctcttggcaggtactcagcgaatgaatgctgtatatgttgggtgcaaagttccctactt
cctgtgacttcagctctgttttacaataaaatcttgaaaatgcctaaaaaaaaaaaaaaaaaaaaaa
aaaaaaaaaaaaaaaaaaaaaaaaaaa.

Human IL-1Ra, transcript 2, is encoded by the following amino acid sequence (NCBI Accession No. NM_173841 and SEQ ID NO: 8):

MALADLYEEGGGGGGEGEDNADSKETICRPSGRKSSKMQAFRIWDVNQKTFYLRN
NQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVN
ITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGV
MVTKFYFQEDE.

Human IL-1Ra, transcript 3, is encoded by the following mRNA sequence (NCBI Accession No. NM_000577 and SEQ ID NO: 9):

gggcagctccaccctgggagggactgtggcccaggtactgcccgggtgctactttatgggcagcagct
cagttgagttagagtctggaagacctcagaagacctcctgtcctatgaggccctcccc**ATG**gctttag
agacgatctgccgaccctctgggagaaaatccagcaagatgcaagccttcagaatctgggatgttaac
cagaagaccttctatctgaggaacaaccaactagttgctggatacttgcaaggaccaaatgtcaattt
agaagaaaagatagatgtggtacccattgagcctcatgctctgttcttgggaatccatggagggaaga
tgtgcctgtcctgtgtcaagtctggtgatgagaccagactccagctggaggcagttaacatcactgac
ctgagcgagaacagaaagcaggacaagcgcttcgccttcatccgctcagacagcggccccaccaccag
ttttgagtctgccgcctgccccggttggttcctctgcacagcgatggaagctgaccagcccgtcagcc
tcaccaatatgcctgacgaaggcgtcatggtcaccaaattctacttccaggaggacgagtagtactgc
ccaggcctgcctgttcccattcttgcatggcaaggactgcagggactgccagtccccctgccccaggg
ctcccggctatgggggcactgaggaccagccattgaggggtggaccctcagaaggcgtcacaagaacc
tggtcacaggactctgcctcctcttcaactgaccagcctccatgctgcctccagaatggtctttctaa
tgtgtgaatcagagcacagcagcccctgcacaaagcccttccatgtcgcctctgcattcaggatcaaa
ccccgaccacctgcccaacctgctctcctcttgccactgcctcttcctccctcattccaccttcccat
gccctggatccatcaggccacttgatgacccccaaccaagtggctcccacaccctgttttacaaaaaa
gaaaagaccagtccatgagggaggtttttaagggtttgtggaaaatgaaaattaggatttcatgattt
tttttttcagtccccgtgaaggagagcccttcatttggagattatgttctttcggggagaggctgag
gacttaaaatattcctgcatttgtgaaatgatggtgaaagtaagtggtagcttttcccttctttttct
tctttttttgtgatgtcccaacttgtaaaaattaaaagttatggtactatgttagccccataatttttt
ttttttcctttaaaacacttccataatctggactcctctgtccaggcactgctgcccagcctccaagc
tccatctccactccagatttttacagctgcctgcagtactttacctcctatcagaagtttctcagct
cccaaggctctgagcaaatgtggctcctgggggttctttcttcctctgctgaaggaataaattgctcc
ttgacattgtagagcttctggcacttggagacttgtatgaaagatggctgtgcctctgcctgtctccc
ccaccgggctgggagctctgcagagcaggaaacatgactcgtatatgtctcaggtccctgcagggcca
agcacctagcctcgctcttggcaggtactcagcgaatgaatgctgtatatgttgggtgcaaagttccc
tacttcctgtgacttcagctctgttttacaataaaatcttgaaaatgcctaaaaaaaaaaaaaaaaaa
aaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa.

Human IL-1Ra, transcript 3, is encoded by the following amino acid sequence (NCBI Accession No. NM_000577 and SEQ ID NO: 10):

MALETICRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVV
PIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPT
TSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE.

Human IL-1Ra, transcript 4, is encoded by the following mRNA sequence (NCBI Accession No. NM_173843 and SEQ ID NO: 11):

gggcagctccaccctgggagggactgtggcccaggtactgcccgggtgctactttatgggcagcagct
cagttgagttagagtctggaagacctcagaagacctcctgtcctatgaggccctccccatggctttag
ggggattataaaactaatcatcaaagccaagaaggcaagagcaagcatgtaccgctgaaaacacaaga
taactgcataagtaatgactttcagtgcagattcatagctaacccataaactgctggggcaaaaatca
tcttggaaggctctgaacctcagaaaggattcacaagacgatctgccgaccctctgggagaaaatcca
gcaag**ATG**caagccttcagaatctgggatgttaaccagaagaccttctatctgaggaacaaccaacta
gttgctggatacttgcaaggaccaaatgtcaatttagaagaaaagatagatgtggtacccattgagcc
tcatgctctgttcttgggaatccatggagggaagatgtgcctgtcctgtgtcaagtctggtgatgaga
ccagactccagctggaggcagttaacatcactgacctgagcgagaacagaaagcaggacaagcgcttc
gccttcatccgctcagacagcggccccaccaccagttttgagtctgccgcctgccccggttggttcct
ctgcacagcgatggaagctgaccagcccgtcagcctcaccaatatgcctgacgaaggcgtcatggtca
ccaaattctacttccaggaggacgagtagtactgcccaggcctgcctgttcccattcttgcatggcaa
ggactgcagggactgccagtccccctgccccagggctcccggctatgggggcactgaggaccagccat
tgaggggtggaccctcagaaggcgtcacaagaacctggtcacaggactctgcctcctcttcaactgac
cagcctccatgctgcctccagaatggtctttctaatgtgtgaatcagagcacagcagcccctgcacaa
agcccttccatgtcgcctctgcattcaggatcaaaccccgaccacctgcccaacctgctctcctcttg
ccactgcctcttcctccctcattccaccttcccatgccctggatccatcaggccacttgatgaccccc
aaccaagtggctcccacaccctgttttacaaaaaagaaaagaccagtccatgagggaggtttttaagg
gtttgtggaaaatgaaaattaggatttcatgatttttttttttcagtccccgtgaaggagagcccttc
atttggagattatgttctttcggggagaggctgaggacttaaaatattcctgcatttgtgaaatgatg
gtgaaagtaagtggtagcttttcccttctttttcttctttttttgtgatgtcccaacttgtaaaaatt
aaaagttatggtactatgttagccccataattttttttttccttttaaaacacttccataatctggac
tcctctgtccaggcactgctgcccagcctccaagctccatctccactccagatttttacagctgcct
gcagtactttacctcctatcagaagtttctcagctcccaaggctctgagcaaatgtggctcctggggg
ttctttcttcctctgctgaaggaataaattgctccttgacattgtagagcttctggcacttggagact
tgtatgaaagatggctgtgcctctgcctgtctcccccaccgggctgggagctctgcagagcaggaaac
atgactcgtatatgtctcaggtccctgcagggccaagcacctagcctcgctcttggcaggtactcagc
gaatgaatgctgtatatgttgggtgcaaagttccctacttcctgtgacttcagctctgttttacaata
aaatcttgaaaatgcctaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa
a.

Human IL-1Ra, transcript 4, is encoded by the following amino acid sequence (NCBI Accession No. NM_173843 and SEQ ID NO: 12):

MQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKM
CLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCT
AMEADQPVSLTNMPDEGVMVTKFYFQEDE.

Human intracellular IL-1Ra, icIL-1Ra, is encoded by the following mRNA sequence (NCBI Accession No. M55646 and SEQ ID NO: 13):

agctccaccctgggagggactgtggcccaggtactgcccgggtgctactttatgggcagcagctcagt
tgagttagagtctggaagacctcagaagacctcctgtcctatgaggccctcccc**ATG**gctttagagac
gatctgccgaccctctgggagaaaatccagcaagatgcaagccttcagaatctgggatgttaaccaga
agaccttctatctgaggaacaaccaactagttgctggatacttgcaaggaccaaatgtcaatttagaa
gaaaagatagatgtggtacccattgagcctcatgctctgttcttgggaatccatggagggaagatgtg
cctgtcctgtgtcaagtctggtgatgagaccagactccagctggaggcagttaacatcactgacctga
gcgagaacagaaagcaggacaagcgcttcgccttcatccgctcagacagtggccccaccaccagtttt
gagtctgccgcctgccccggttggttcctctgcacagcgatggaagctgaccagcccgtcagcctcac
caatatgcctgacgaaggcgtcatggtcaccaaattctacttccaggaggacgagtag.

Human intracellular IL-1Ra, icIL-1Ra, is encoded by the following amino acid sequence (NCBI Accession No. M55646 and SEQ ID NO: 14):

MALETICRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVV PIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPT TSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE.

Human Recombinant IL-1Ra:

A recombinant form of human IL-1Ra (rHuIL-1Ra) was developed and tested in animal models for arthritis. This form of rHuIL-1Ra is also known as Anakinra or Kineret® differs from the native nonglycosylated IL-1Ra by the addition of an N-terminal methionine. It binds to

IL-1R type I with the same affinity as IL-1ß. Kineret® consists of 153 amino acids and has a molecular weight of 17.3 kilodaltons. It is produced by recombinant DNA technology using an *E. coli* bacterial expression system.

Anakinra has been investigated in several conditions considered mediated at least in part via IL-1. Some evidence suggests involvement of IL-1 in the pathogenesis of rheumatoid arthritis and septic shock (Jiang, Y. et al. 2000. Arthritis Rheum. 43:1001-1009; Fisher, C.J. et al.1994. JAMA.271:1836-1843; Okusawa, S. et al. 1988. J Clin Invest. 81:1162-1172; Bresnihan, B. et al. 1998. Rheum Dis Clin North Am. 24(3):615-628; Dayer, J.M. et al. 2001. Curr Opin Rheumatol. 13:170-176; Edwards, C.K. 2001. J Clin Rheumatol. 7:S17-S24).

Anakinra has been approved by the FDA for the reduction in signs and symptoms of moderately to severely active rheumatoid arthritis in patients 18 years of age or older who have failed one or more disease-modifying antirheumatic drugs. Considering its high safety profile, administration of Anakinra has also been used in the treatment of arthritis in patients with Juvenile rheumatoid arthritis (Reiff, A. 2005. Curr Rheumatol Rep. 7:434-40). Other indications include prevention of graft-versus-host disease (GVHD) after bone marrow transplantation (Antin, J.H. et al. 1994. Blood.84:1342-8), uveitis (Teoh, S.C. et al. 2007. Br J Opthalmol. 91: 263-4) osteoarthritis (Caron, J.P. et al. 1996. Arthritis Rheum. 39:1535-44), asthma, inflammatory bowel disease, acute pancreatitis (Hynninen, M. et al. 1999. J Crit Care. 14:63-8), psoriasis, and type II diabetes mellitus (Larsen, C.M. et al. 2007. N Engl J. Med. 356:1517-26). The systemic safety profile of IL-1Ra is extremely favorable, especially in comparison to other immunosuppressive treatments such as TNF-α blockers, cytotoxic agents, or even steroids.

Topical human recombinant IL-1Ra has been successfully used for prevention of corneal transplant rejection (Yamada, J. et al. 2000. Invest Opthalmol Vis Sci. 41:4203-8) and allergic conjunctivitis (Keane-Myers, A.M. et al. 1999. Invest Opthalmol Vis Sci. 40:3041-6) in experimental animal models. Similarly, using topical IL-1Ra significantly decreases corneal inflammation and leads to enhanced corneal transparency in the rat model of corneal alkali injury (Yamada, J. et al. 2003. Exp Eye Res. 76:161-7).

A recombinant form of human IL-1Ra (rHuIL-1Ra) was developed and approved for use in humans by subcutaneous injection for the treatment of arthritis. This form of rHuIL-1Ra, also known as Anakinra or Kineret® (Amgen Inc.), differs from the native nonglycosylated IL-1Ra by the addition of an N-terminal methionine. It binds to human IL-1R, type 1, (IL-1R1) with the same affinity as IL-1 ß. Kineret® consists of 153 amino acids (see SEQ ID NO: 16) and has a molecular weight of 17.3 kilodaltons. It is produced by recombinant DNA technology using an E. coli bacterial expression system.

Compositions of the invention comprise one or more regions of SEQ ID NO: 15 or SEQ ID NO: 16. Furthermore, compositions of the invention comprise the entire sequence of either SEQ ID NO: 15 or SEQ ID NO: 16.

Anakinra/Kineret® is encoded by the following mRNA sequence (NCBI Accession No. M55646 and SEQ ID NO: 15):

agctccaccctgggagggactgtggcccaggtactgcccgggtgctactttatgggcagcagctcagt
tgagttagagtctggaagacctcagaagacctcctgtcctatgaggccctcccc**ATG**gctttagagac
gatctgccgaccctctgggagaaaatccagcaagatgcaagccttcagaatctgggatgttaaccaga
agaccttctatctgaggaacaaccaactagttgctggatacttgcaaggaccaaatgtcaatttagaa
gaaaagatagatgtggtacccattgagcctcatgctctgttcttgggaatccatggagggaagatgtg
cctgtcctgtgtcaagtctggtgatgagaccagactccagctggaggcagttaacatcactgacctga
gcgagaacagaaagcaggacaagcgcttcgccttcatccgctcagacagtggccccaccaccagtttt
gagtctgccgcctgccccggttggttcctctgcacagcgatggaagctgaccagcccgtcagcctcac
caatatgcctgacgaaggcgtcatggtcaccaaattctacttccaggaggacgagtag.

Anakinra/Kineret® is encoded by the following polypeptide sequence (DrugBank Accession No. BTD00060 and SEQ ID NO: 16):

MRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHA
LFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFES
AACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE

IL-1 Receptors:

The composition of the present invention comprises a polynucleotide, a polypeptide, an antibody, a compound, or a small molecule with means to inhibit the transcription, transcript stability, translation, modification, localization, secretion, or function of a

polynucleotide or polypeptide encoding the IL-1 receptor, either type 1 or 2. In the present application the IL-1 Receptor, type 1 (IL-1R1), is defined by the polynucleotide sequence of SEQ ID NO: 17 or the polypeptide sequence of SEQ ID NO: 18. In the present application the IL-1 Receptor, type 2 (IL-1R2), transcript variants 1 and 2, are defined by the polynucleotide sequences of

SEQ ID NO: 19 and 20, or the polypeptide sequence of SEQ ID NO: 21. IL-1R2 can function as a "decoy" receptor which binds IL-1 cytokines and inhibits IL-1R1. Polynucleotide or polypeptide compositions bind to one or more region(s) of IL-1R1 or IL-1R2, and associated isoforms, comprised by SEQ ID NO: 17-21.

IL-1R1 is encoded by the following mRNA sequence (NCBI Accession No. NM_000877 and SEQ ID NO: 17):

tagacgcaccctctgaagatggtgactccctcctgagaagctggacccctttggtaaaagacaaggcct
tctccaagaagaat**ATG**aaagtgttactcagacttatttgtttcatagctctactgatttcttctctg
gaggctgataaatgcaaggaacgtgaagaaaaaataattttagtgtcatctgcaaatgaaattgatgt
tcgtccctgtcctcttaacccaaatgaacacaaaggcactataacttggtataaagatgacagcaaga
cacctgtatctacagaacaagcctccaggattcatcaacacaaagagaaactttggtttgttcctgct
aaggtggaggattcaggacattactattgcgtggtaagaaattcatcttactgcctcagaattaaaat
aagtgcaaaatttgtggagaatgagcctaacttatgttataatgcacaagccatatttaagcagaaac
tacccgttgcaggagacggaggacttgtgtgcccttatatggagtttttaaaaatgaaaataatgag
ttacctaaattacagtggtataaggattgcaaacctctacttcttgacaatatacactttagtggagt
caaagataggctcatcgtgatgaatgtggctgaaaagcatagagggaactatacttgtcatgcatcct
acacatacttgggcaagcaatatcctattacccgggtaatagaatttattactctagaggaaaacaaa
cccacaaggcctgtgattgtgagcccagctaatgagacaatggaagtagacttgggatcccagataca
attgatctgtaatgtcaccggccagttgagtgacattgcttactggaagtggaatgggtcagtaattg
atgaagatgacccagtgctaggggaagactattacagtgtggaaaatcctgcaaacaaaagaaggagt
accctcatcacagtgcttaatatatcggaaattgaaagtagattttataaacatccatttacctgttt
tgccaagaatacacatggtatagatgcagcatatatccagttaatatatccagtcactaatttccaga
agcacatgattggtatatgtgtcacgttgacagtcataattgtgtgttctgttttcatctataaaatc
ttcaagattgacattgtgctttggtacagggattcctgctatgattttctcccaataaaagcttcaga
tggaaagacctatgacgcatatatactgtatccaaagactgttggggaagggtctacctctgactgtg
atatttttgtgtttaaagtcttgcctgaggtcttggaaaaacagtgtggatataagctgttcatttat
ggaagggatgactacgttggggaagacattgttgaggtcattaatgaaaacgtaaagaaaagcagaag
actgattatcattttagtcagagaaacatcaggcttcagctggctgggtggttcatctgaagagcaaa
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gactatgagaaaatgccagaatcgattaaattcattaagcagaaacatggggctatccgctggtcagg
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tatccctgaggtcacctggaatcagattattaagggaataagccatgacgtcaatagcagcccagggc
acttcagagtagagggcttgggaagatcttttaaaaaggcagtaggcccggtgtggtggctcacgcct
ataatcccagcactttgggaggctgaagtgggtggatcaccagaggtcaggagttcgagaccagccca
gccaacatggcaaaaccccatctctactaaaaatacaaaaatgagctaggcatggtggcacacgcctg
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gccgagtttgggccactgcactctagcctggcaacagagcaagactccgtctcaaaaaaagggcaata
aatgccctctctgaatgtttgaactgccaagaaaaggcatggagacagcgaactagaagaaagggcaa
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ttgtctggggaccctgtagagtcactgaccctggagcggctctcctgagaggtgctgcaggcaaagtg
agactgacacctcactgaggaagggagacatattcttggagaactttccatctgcttgtattttccat

acacatccccagccagaagttagtgtccgaagaccgaattttattttacagagcttgaaaactcactt
caatgaacaaagggattctccaggattccaaagttttgaagtcatcttagctttccacaggagggaga
gaacttaaaaaagcaacagtagcagggaattgatccacttcttaatgctttcctccctggcatgacca
tcctgtcctttgttattatcctgcattttacgtctttggaggaacagctccctagtggcttcctccgt
ctgcaatgtcccttgcacagcccacacatgaaccatccttcccatgatgccgctcttctgtcatcccg
ctcctgctgaaacacctcccaggggctccacctgttcaggagctgaagcccatgctttcccaccagca
tgtcactcccagaccacctccctgccctgtcctccagcttcccctcgctgtcctgctgtgtgaattcc
caggttggcctggtggccatgtcgcctgcccccagcactcctctgtctctgctcttgcctcgaccctt
cctcctcctttgcctaggaggccttctcgcattttctctagctgatcagaatttaccaaaattcaga
acatcctccaattccacagtctctgggagactttccctaagaggcgacttcctctccagccttctctc
tctggtcaggcccactgcagagatggtggtgagcacatctgggaggctggtctccctccagctggaat
tgctgctctctgagggagaggctgtggtggctgtctctgtccctcactgccttccaggagcaatttgc
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gcaattattctaattttatatatagagaaagtgacctatttttaaaaaaatcacactctaagttcta
ttgaacctaggacttgagcctccatttctggcttctagtctggtgttctgagtacttgatttcaggtc
aataacggtcccccctcactccacactggcacgtttgtgagaagaaatgacattttgctaggaagtga
ccgagtctaggaatgcttttattcaagacaccaaattccaaacttctaaatgttggaattttcaaaaa
ttgtgtttagattttatgaaaaactcttctactttcatctattctttccctagaggcaaacatttctt
aaaatgtttcattttcattaaaaatgaaagccaaatttatatgccaccgattgcaggacacaagcaca
gttttaagagttgtatgaacatggagaggacttttggtttttatatttctcgtatttaatatgggtga
acaccaacttttatttggaataataatttttcctcctaaacaaaaacacattgagtttaagtctctgac
tcttgcctttccacctgctttctcctgggcccgctttgcctgcttgaaggaacagtgctgttctggag
ctgctgttccaacagacagggcctagctttcatttgacacacagactacagccagaagcccatggagc
agggatgtcacgtcttgaaaagcctattagatgttttacaaatttaattttgcagattattttagtct
gtcatccagaaaatgtgtcagcatgcatagtgctaagaaagcaagccaatttggaaacttaggttagt
gacaaaattggccagagagtgggggtgatgatgaccaagaattacaagtagaatggcagctggaattt
aaggagggacaagaatcaatggataagcgtgggtggaggaagatccaaacagaaaagtgcaaagttat
tccccatcttccaagggttgaattctggaggaagaagacacattcctagttccccgtgaacttccttt
gacttattgtccccactaaaacaaaacaaaaaacttttaatgccttccacattaattagattttcttg
cagtttttttatggcatttttttaaagatgccctaagtgttgaagaagagtttgcaaatgcaacaaaa
tatttaattaccggttgttaaaactggtttagcacaatttatattttccctctcttgcctttcttatt
tgcaataaaaggtattgagccatttttttaaatgacattttgataaattatgtttgtactagttgatg
aaggagtttttttttaacctgtttatataatttgcagcagaagccaaatttttttgtatattaaagcac
caaattcatgtacagcatgcatcacggatcaatagactgtacttattttccaataaaattttcaaact
ttgtactgttaaa.

IL-1R1 is encoded by the following amino acid sequence (NCBI Accession No. NM_000877 and SEQ ID NO: 18):

MKVLLRLICFIALLISSLEADKCKEREEKIILVSSANEIDVRPCPLNPNEHKGTITWYKD
DSKTPVSTEQASRIHQHKEKLWFVPAKVEDSGHYYCVVRNSSYCLRIKISAKFVENE
PNLCYNAQAIFKQKLPVAGDGGLVCPYMEFFKNENNELPKLQWYKDCKPLLLDNIH
FSGVKDRLIVMNVAEKHRGNYTCHASYTYLGKQYPITRVIEFITLEENKPTRPVIVSP
ANETMEVDLGSQIQLICNVTGQLSDIAYWKWNGSVIDEDDPVLGEDYYSVENPANK
RRSTLITVLNISEIESRFYKHPFTCFAKNTHGIDAAYIQLIYPVTNFQKHMIGICVTLTVI
IVCSVFIYKIFKIDIVLWYRDSCYDFLPIKASDGKTYDAYILYPKTVGEGSTSDCDIFVF
KVLPEVLEKQCGYKLFIYGRDDYVGEDIVEVINENVKKSRRLIIILVRETSGFSWLGGS
SEEQIAMYNALVQDGIKVVLLELEKIQDYEKMPESIKFIKQKHGAIRWSGDFTQGPQS
AKTRFWKNVRYHMPVQRRSPSSKHQLLSPATKEKLQREAHVPLG.

IL-1R2, transcript variant 1, is encoded by the following mRNA sequence (NCBI Accession No. NM_004633 and SEQ ID NO: 19):

cccgtgaggaggaaaaggtgtgtccgctgccacccagtgtgagcgggtgacaccacccggttaggaaa
tcccagctcccaagagggtataaatccctgctttactgctgagctcctgctggaggtgaaagtctggc
ctggcagccttccccaggtgagcagcaacaaggccacgtgctgctgggtctcagtcctccacttcccg
tgtcctctggaagttgtcaggagca**ATG**ttgcgcttgtacgtgttggtaatgggagtttctgccttca
cccttcagcctgcggcacacacaggggctgccagaagctgccggtttcgtgggaggcattacaagcgg
gagttcaggctggaaggggagcctgtagccctgaggtgcccccaggtgccctactggttgtgggcctc
tgtcagcccccgcatcaacctgacatggcataaaaatgactctgctaggacggtcccaggagaagaag
agacacggatgtgggcccaggacggtgctctgtggcttctgccagccttgcaggaggactctggcacc
tacgtctgcactactagaaatgcttcttactgtgacaaaatgtccattgagctcagagtttttgagaa
tacagatgctttcctgccgttcatctcatacccgcaaattttaaccttgtcaacctctggggtattag
tatgccctgacctgagtgaattcacccgtgacaaaactgacgtgaagattcaatggtacaaggattct
cttcttttggataaagacaatgagaaatttctaagtgtgaggggaccactcacttactcgtacacga
tgtggccctggaagatgctggctattaccgctgtgtcctgacatttgcccatgaaggccagcaataca
acatcactaggagtattgagctacgcatcaagaaaaaaaaagaagagaccattcctgtgatcatttcc
cccctcaagaccatatcagcttctctggggtcaagactgacaatcccgtgtaaggtgtttctgggaac
cggcacacccttaaccaccatgctgtggtggacggccaatgacacccacatagagagcgcctacccgg
gaggccgcgtgaccgaggggccacgccaggaatattcagaaaataatgagaactacattgaagtgcca
ttgatttttgatcctgtcacaagagaggatttgcacatggattttaaatgtgttgtccataataccct
gagttttcagacactacgcaccacagtcaaggaagcctcctccacgttctcctggggcattgtgctgg
ccccactttcactggccttcttggttttgggggaatatggatgcacagacggtgcaaacacagaact
ggaaaagcagatggtctgactgtgctatggcctcatcatcaagactttcaatcctatcccaagtgaaa
taaatggaatgaaataattcaaacacaaaaaaaaaaaaaaaaaaaaaaaaaaaa.

IL-1R2, transcript variant 2, is encoded by the following mRNA sequence (NCBI Accession No. NM_173343 and SEQ ID NO: 20):

gggatgggagatactgttgtggtcacctctggaaaatacattctgctactcttaaaaactagtgacgc
tcatacaaatcaacagaaagagcttctgaaggaagactttaaagctgcttctgccacgtgctgctggg
tctcagtcctccacttcccgtgtcctctggaagttgtcaggagca**ATG**ttgcgcttgtacgtgttggt
aatgggagtttctgccttcacccttcagcctgcggcacacacaggggctgccagaagctgccggtttc
gtgggaggcattacaagcgggagttcaggctggaaggggagcctgtagccctgaggtgcccccaggtg
ccctactggttgtgggcctctgtcagcccccgcatcaacctgacatggcataaaaatgactctgctag
gacggtcccaggagaagaagagacacggatgtgggcccaggacggtgctctgtggcttctgccagcct
tgcaggaggactctggcacctacgtctgcactactagaaatgcttcttactgtgacaaaatgtccatt
gagctcagagtttttgagaatacagatgctttcctgccgttcatctcatacccgcaaattttaaccttt
gtcaacctctggggtattagtatgccctgacctgagtgaattcacccgtgacaaaactgacgtgaaga
ttcaatggtacaaggattctcttcttttggataaagacaatgagaaatttctaagtgtgaggggacc
actcacttactcgtacacgatgtggccctggaagatgctggctattaccgctgtgtcctgacatttgc
ccatgaaggccagcaatacaacatcactaggagtattgagctacgcatcaagaaaaaaaaagaagaga
ccattcctgtgatcatttcccccctcaagaccatatcagcttctctggggtcaagactgacaatcccg
tgtaaggtgtttctgggaaccggcacacccttaaccaccatgctgtggtggacggccaatgacaccca
catagagagcgcctacccgggaggccgcgtgaccgaggggccacgccaggaatattcagaaaataatg
agaactacattgaagtgccattgattttgatcctgtcacaagagaggatttgcacatggattttaaa
tgtgttgtccataataccctgagttttcagacactacgcaccacagtcaaggaagcctcctccacgtt
ctcctggggcattgtgctggccccactttcactggccttcttggttttgggggaatatggatgcaca
gacggtgcaaacacagaactggaaaagcagatggtctgactgtgctatggcctcatcatcaagacttt
caatcctatcccaagtgaaataaatggaatgaaataattcaaacacaaaaaaaaaaaaaaaaaaaaa
aaaaaaaa.

IL-1R2, transcript variants 1 and 2, are encoded by the following amino acid sequence (NCBI Accession No. NM_004633, NM_173343, and SEQ ID NO: 21):

MLRLYVLVMGVSAFTLQPAAHTGAARSCRFRGRHYKREFRLEGEPVALRCPQVPY
WLWASVSPRINLTWHKNDSARTVPGEEETRMWAQDGALWLLPALQEDSGTYVCTT

RNASYCDKMSIELRVFENTDAFLPFISYPQILTLSTSGVLVCPDLSEFTRDKTDVKIQW
YKDSLLLDKDNEKFLSVRGTTHLLVHDVALEDAGYYRCVLTFAHEGQQYNITRSIEL
RIKKKKEETIPVIISPLKTISASLGSRLTIPCKVFLGTGTPLTTMLWWTANDTHIESAYP
GGRVTEGPRQEYSENNENYIEVPLIFDPVTREDLHMDFKCVVHNTLSFQTLRTTVKE
ASSTFSWGIVLAPLSLAFLVLGGIWMHRRCKHRTGKADGLTVLWPHHQDFQSYPK.

Interleukin-1 Receptor (type 2) antagonist (IL-1Ra3):

The present invention comprises compositions with means to inhibit or enhance the activity of the human IL-1R2. Compositions that comprise the IL-1R2 antagonist, IL-1Ra3, have either agonist or antagonist activity regarding the efficacy of IL-1R1 function. The composition comprises a polynucleotide, a polypeptide, an antibody, a compound, or a small molecule with means to inhibit the transcription, transcript stability, translation, modification, localization, secretion, or function of a polynucleotide or polypeptide encoding IL-1Ra3. The inhibitory polynucleotide or polypeptide composition binds to one or more region(s) of IL-1Ra3 comprised by SEQ ID NO: 22 and SEQ ID NO: 23.

IL-1Ra3 is encoded by a region or the entirety of the following mRNA sequence (NCBI Accession No. AF_057168 and SEQ ID NO: 22): (for this sequence, the bolded and capitalized codon does not encode methionine, but rather represents the codon that encodes the first amino acid of the corresponding polypeptide)

cagaagacctcctgtcctatgaggccctccccatggctttaggtaagctccttccactctcatttttt
cacctgagaaatgagagaggaaaatgtctacaattggtgtttatcaaatgctttcaggctctggtgag
caagcgtccaggaaaatgtcaagcgcatggagctccaggcctgtctgggggatctgggcacggggagg
catccatgggagaccatgcaggcactctgaggcaggggctgcaagctagtgcctgctggggcagcagg
tgaacagagaggtgtaactgctgtgacagaagtcatggagtccttggagtgtgagggtcattttccac
tgttgatagaatagggaaattggtgaaatagccctgttaaatgagagaaagaacagtgtgagctcaat
gagaaatactaatagaatgtggcactgagccacaaggtctgagggttgattgataaggaagggtgggg
actgtggagaattaagggcttggcacaggtcagttccaccagttgtcacaagagaatgcaggctcagg
tggccagaacttctcgcttttccagaagagtccgatattctgatttcattatatatagtattctgatt
aaaccagacaataaagcaagcagataaaatatttaaagtataagctgccagtttgcaacctccggtta
ggatttgtgtggggcaaagaaaaaaactctcaggatcattggtatgtagactctaattttaagtttct
aatttaaaattggcccctgaggctgggcgtggtggctcacacctgtaatcccagcattttgggaggcc
aaggtgggtggatctcttgaggtcaagagttcaaggcctgcctggccaacatggtgaaaccctgtctc
tattaaaaatacaaaaattagctgggcatggtggtgcatgtctgcaatcttagctacttgggtagcta
aggcaggagaattgctggaacccgggaggtagaggttgcagtgaatggagatcacaccactgcactcc
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ataggcctctaatgagcaggccattctcctttctgggtcttactttccttgcactcctttctgggtgt
taagaggaggtctagaggaagctggacaactcttagcttgtagtaagcacagtggaagtatcagctct
taatgggtcatggacacgttacgaagctaggcgccgtgctgagcactttacatggtttatcccactga
accctctcaataaccctatgaggaagggctattattgctcacattttcagaagaggaaatggatatag
agagattagataatttgcccatggccagacagctagtataagaggaggaggtggattgactgcagaca
ttctgtcttcaaaccactacactatgctatggaggcacagagacttaatgaaatcatggagaggggaa
ttgctttgtcaaccacaagcagttattccgggggcagcagatcctcccctgtcccccagtggtacaat
ggtccctggtgggttgtgctacaatgttagcccatggtcttatgtgtttttcaaatgtgtaaagtagg
atgctggaaccactcttagaaccagataccaatacattgtgaagaaataaatctctgtgcttaaaact
ggttcatcccaaaatattttgaactgacacacaataggtgctaaataaatgtgtgttaacttgaattg
gattgaattcgggaaaaaagtgcaataagcttagtgaagacaccatgttccctgggtagaggaaccac
attctccatctaaggccaggagtatgggaggtatcaatgtttgcccagcacagaacagggtgccaaga

agagaaaagttgacggggtgcatactctgactggaaactggaagggtgagaacagagggtaaaggata
gagatggaaccatgtgcatacactttgtgttaccttggacaagtcattcatttctctggacctctgct
ttctctctacacaatggggtcccaccacttcccttacagctgacttgtatgaagaaggaggtggagga
ggaggagaaggtgaagacaatg**CTG**actcaaagggtaaattatttttaggatccaagtttgaaaacaa
ttttaggctactagatatgaacaacatcttgattatgtagttgaaggaaattaaagatgaatggttta
attaaaaattaatcagaatgaaaacgattgattactaatatatctgcaatggtttatttcctgagtg
gcagactcactaaggtttttgaatactcctgtgtgattgctctatgtatgtatgtatgtatgtatgta
tgcatgtatctatctatctgttgtctaatagaatggatcacatctctgctaataaaaacactacactg
gcagggtacaattataatcattaactgtgcctggaatttgcagcagcagccaccagaggtaccagtgc
cctttaagggttcataatttagaataatccaattatctgagttttcagggactgaggggtttggcaa
ggtgtagaactttcagtaataaagtcaagaaagtcctggacaaaccaaggtagttggtcactctagtc
cataaccaggtaaagagctttccctgtaacctgtgtaaggttttagaatcatttctttccttattacc
aaaaatcctccccaaattttcaagaaattatgaactaaatagttactctatgagataggagttcagcc
caaaagaaacaccataagaacaaatataattcttgcttatgttaaccatgcaatgaagcagagagaaa
aagtcagtggcctctttaggaggactgtagtgtgggaagaaataactaaactgggtttcaatcctggc
ctggccaggatctggagcaagtgagttaatctttctaagccttgagtagtttataaaagaatggccac
tccatagacagagtagcctgaaccttgagttcttctataaagtcactatgaatttatactcattttga
aagtgggtgtcaatatgtctgtccactttgcacagctgttatgtggacaaaaggagatctgtgtgaaa
gtgtaacacagagcctaaactataacaggtaagcaacacagttgtccct.

One or more isoforms of IL-1Ra3 comprise the following amino acid sequence (NCBI Accession No. AF_057168 and SEQ ID NO: 23):
DLYEEGGGGGGEGEDNADSK.

Interleukin-1 Receptor Accessory Protein (IL-1RAP):

Compositions that inhibit the activity of human IL-1RAP inhibit IL-1RAP binding to an IL-1 cytokine or an IL-1 receptor, and subsequent transduction of downstream intracellular signals. Compositions that comprise an inhibitor of IL-1RAP function antagonize the activity of an IL-1 receptor. The composition comprises a polynucleotide, a polypeptide, an antibody, a compound, or a small molecule with means to inhibit the transcription, transcript stability, translation, modification, localization, secretion, or function of a polynucleotide or polypeptide encoding IL-1RAP. The inhibitory polynucleotide or polypeptide composition binds to one or more region(s) of IL-1RAP, and associated isoforms, comprised by SEQ ID NO: 24-27.
IL-1RAP, transcript variant 1, is encoded by the following mRNA sequence (NCBI Accession No. NM_002182 and SEQ ID NO: 24):

tgccgggatccaggtctccggggtccgctttggccagaggcgcggaaggaagcagtgcccggcgacac
tgcacccatcccggctgcttttgctgcgccctctcagcttcccaagaaaggcatcgtcatgtgatcat
cacctaagaactagaacatcagcaggccctagaagcctcactcttgcccctcccttaatatctcaaa
gg**ATG**acacttctgtggtgtgtagtgagtctctacttttatggaatcctgcaaagtgatgcctcagaa
cgctgcgatgactggggactagacaccatgaggcaaatccaagtgtttgaagatgagccagctcgcat
caagtgcccactctttgaacacttcttgaaattcaactacagcacagcccattcagctggccttactc
tgatctggtattggactaggcaggaccgggaccttgaggagccaattaacttccgcctccccgagaac
cgcattagtaaggagaaagatgtgctgtggttccggcccactctcctcaatgacactggcaactatac
ctgcatgttaaggaacactacatattgcagcaaagttgcatttcccttggaagttgttcaaaaagaca

gctgtttcaattcccccatgaaactcccagtgcataaactgtatatagaatatggcattcagaggatc
acttgtccaaatgtagatggatattttccttccagtgtcaaaccgactatcacttggtatatgggctg
ttataaaatacagaattttaataatgtaatacccgaaggtatgaacttgagtttcctcattgccttaa
tttcaaataatggaaattacacatgtgttgttacatatccagaaaatggacgtacgtttcatctcacc
aggactctgactgtaaaggtagtaggctctccaaaaaatgcagtgccccctgtgatccattcacctaa
tgatcatgtggtctatgagaaagaaccaggagaggagctactcattccctgtacggtctattttagtt
ttctgatggattctcgcaatgaggtttggtggaccattgatggaaaaaaacctgatgacatcactatt
gatgtcaccattaacgaaagtataagtcatagtagaacagaagatgaaacaagaactcagattttgag
catcaagaaagttacctctgaggatctcaagcgcagctatgtctgtcatgctagaagtgccaaaggcg
aagttccaaagcagccaaggtgaagcagaaagtgccagctccaagatacacagtggaactggcttgtg
gttttggagccacagtcctgctagtggtgattctcattgttgtttaccatgtttactggctagagatg
gtcctattttaccgggctcattttggaacagatgaaaccattttagatggaaaagagtatgatattta
tgtatcctatgcaaggaatgcggaagaagaagaatttgtattactgaccctccgtggagttttggaga
atgaatttggatacaagctgtgcatctttgaccgagacagtctgcctgggggaattgtcacagatgag
actttgagcttcattcagaaaagcagacgcctcctggttgttctaagccccaactacgtgctccaggg
aacccaagccctcctggagctcaaggctggcctagaaaatatggcctctcggggcaacatcaacgtca
ttttagtacagtacaaagctgtgaaggaaacgaaggtgaaagagctgaagagggctaagacggtgctc
acggtcattaaatggaaaggggaaaaatccaagtatccacagggcaggttctggaagcagctgcaggt
ggccatgccagtgaagaaaagtcccaggcggtctagcagtgatgagcagggcctctcgtattcatctt
tgaaaaatgtatgaaaggaataatgaaaagggtaaaaagaacaaggggtgctccaggaagaaagagtc
cccccagtcttcattcgcagtttatggtttcataggcaaaaataatggtctaagcctcccaataggga
taaatttagggtgactgtgtggctgactattctgcttcctcaggcaacactaaagtttagaaagatat
catcaacgttctgtcaccagtctctgatgccactatgttctttgcaggcaaagacttgttcaatgcga
atttccccttctacattgtctatccctgtttttatatgtctccattctttttaaaatcttaacatatg
gagcagcctttcctatgaatttaaatatgcctttaaaataagtcactgttgacagggtcatgagtttc
cgagtatagttttcttttatcttatttttactcgtccgttgaaaagataatcaaggcctacatttta
gctgaggataatgaacttttttcctcattcggctgtataatacataaccacagcaagactgacatcca
cttaggatgatacaaagcagtgtaactgaaaatgtttcttttaattgatttaaaggacttgtcttcta
taccacccttgtcctcatctcaggtaatttatgaaatctatgtaaacttgaaaaatatttcttaattt
ttgtttttgctccagtcaattcctgattatccacaggtcaacccacatttttttcattccttctcccta
tctgcttatatcgcattgctcatttagagtttgcaggaggctccatactaggttcagtctgaaagaaa
tctcctaatggtgctatagagagggaggtaacagaaagactcttttagggcatttttctgactcatga
aaagagcacagaaaaggatgtttggcaatttgtcttttaagtcttaaccttgctaatgtgaatactgg
gaaagtgatttttctcactcgtttttgttgctccattgtaaagggcggaggtcagtcttagtggcct
tgagagttgcttttggcattaatattctaagagaattaactgtatttcctgtcacctattcactagtg
caggaaatatacttgctccaaataagtcagtatgagaagtcactgtcaatgaaagttgttttgtttgt
tttcagtaatattttgctgtttttaagacttggaaaactaagtgcagagtttacagagtggtaaatat
ctatgttacatgtagattatacatatatatacacacgtgtatatgagatatatatcttatatctccac
aaacacaaattatatatatacatatccacacacatacattacatatatctgtgtatataaatccacat
gcacatgaaatatatatatatatataatttgtgtgtgtgtatgtgtatgtatatgactttaaatagct
atgggtacaatattaaaaaccactggaactcttgtccagtttttaaattatgtttttactggaatgtt
tttgtgtcagtgttttctgtacatattatttgttaattcacagctcacagagtgatagttgtcatagt
tcttgccttccctaagtttatataaataacttaagtattgctacagtttatctaggttgcagtggcat
ctgctgtgcacagagcttccatggtcactgctaagcagtagccagccatcgggcattaattgatttcc
tactatattcccagcagacacatttagaaactaagctatgttaacctcagtgctcaactatttgaact
gttgagtgataaaggaaacaaatataactgtaaatgaatcttggtatcctgtgaaacagaataattcg
taatttaagaaagcccttatcccggtaacatgaatgttgatgaacaaatgtaaaattatatcctatat
ttaagtacccataataaatcatttccctctataagtgttattgattattttaaattgaaaaaagtttc
acttggatgaaaaaagtagaaaagtaggtcattcttggatctacttttttttagccttattaatattt
ttccctattagaaaccacaattactccctctattaacccttcacttactagaccagaaaagaacttat
tccagataagctttgaatatcaattcttacataaactttaggcaaacagggaatagtctagtcaccaa
aggaccattctcttgccaatgctgcattccttttgcacttttggattccatatttatcccaaatgctg
ttgggcacccctagaaataccttgatgtttttttctatttatatgcctgcctttggtacttaattttac
aaatgctgtaatataaagcatatcaagtttatgtgatacgtatcattgcaagagaatttgtttcaaga
ttttttttttaatgttccagaagatggccaatagagaacattcaagggaaatggggaaacataatttag
agaacaagaacaaaccatgtctcaaatttttttaaaaaaaattaatggttttaaatatatgctatagg

gacgttccatgcccaggttaacaaagaactgtgatatatagagtgtctaattacaaaatcatatacga
tttatttaattctcttctgtattgtaacttagatgattcccaaggactctaataaaaaatcacttcat
tgtatttggaaacaaaaacatcattcattaattacttattttctttccataggttttaatattttgag
agtgtctttttatttcattcatgaacttttgtatttttcatttttcatttgatttgtaaatttactt
atgttaaaaataaaccatttattttcagctttg.

IL-1RAP, transcript variant 1, is encoded by the following amino acid sequence (NCBI Accession No. NM_002182 and SEQ ID NO: 25):

MTLLWCVVSLYFYGILQSDASERCDDWGLDTMRQIQVFEDEPARIKCPLFEHFLKFN
YSTAHSAGLTLIWYWTRQDRDLEEPINFRLPENRISKEKDVLWFRPTLLNDTGNYTC
MLRNTTYCSKVAFPLEVVQKDSCFNSPMKLPVHKLYIEYGIQRITCPNVDGYFPSSVK
PTITWYMGCYKIQNFNNVIPEGMNLSFLIALISNNGNYTCVVTYPENGRTFHLTRTLT
VKVVGSPKNAVPPVIHSPNDHVVYEKEPGEELLIPCTVYFSFLMDSRNEVWWTIDGK
KPDDITIDVTINESISHSRTEDETRTQILSIKKVTSEDLKRSYVCHARSAKGEVAKAAK
VKQKVPAPRYTVELACGFGATVLLVVILIVVYHVYWLEMVLFYRAHFGTDETILDG
KEYDIYVSYARNAEEEEFVLLTLRGVLENEFGYKLCIFDRDSLPGGIVTDETLSFIQKS
RRLLVVLSPNYVLQGTQALLELKAGLENMASRGNINVILVQYKAVKETKVKELKRA
KTVLTVIKWKGEKSKYPQGRFWKQLQVAMPVKKSPRRSSSDEQGLSYSSLKNV.

IL-1RAP, transcript variant 2, is encoded by the following mRNA sequence (NCBI Accession No. NM_134470 and SEQ ID NO: 26):

tgccgggatccaggtctccggggtccgctttggccagaggcgcggaaggaagcagtgcccggcgacac
tgcacccatcccggctgcttttgctgcgccctctcagcttcccaagaaaggcatcgtcatgtgatcat
cacctaagaactagaacatcagcaggccctagaagcctcactcttgcccctcccttaatatctcaaa
gg**ATG**acacttctgtggtgtgtagtgagtctctacttttatggaatcctgcaaagtgatgcctcagaa
cgctgcgatgactggggactagacaccatgaggcaaatccaagtgtttgaagatgagccagctcgcat
caagtgcccactctttgaacacttcttgaaattcaactacagcacagcccattcagctggccttactc
tgatctggtattggactaggcaggaccgggaccttgaggagccaattaacttccgcctccccgagaac
cgcattagtaaggagaaagatgtgctgtggttccggcccactctcctcaatgacactggcaactatac
ctgcatgttaaggaacactacatattgcagcaaagttgcatttcccttggaagttgttcaaaaagaca
gctgtttcaattcccccatgaaactcccagtgcataaactgtatatagaatatggcattcagaggatc
acttgtccaaatgtagatggatattttccttccagtgtcaaaccgactatcacttggtatatgggctg
ttataaaatacagaattttaataatgtaatacccgaaggtatgaacttgagtttcctcattgccttaa
tttcaaataatggaaattacacatgtgttgttacatatccagaaaatggacgtacgtttcatctcacc
aggactctgactgtaaaggtagtaggctctccaaaaaatgcagtgccccctgtgatccattcacctaa
tgatcatgtggtctatgagaaagaaccaggagaggagctactcattccctgtacggtctattttagtt
ttctgatggattctcgcaatgaggtttggtggaccattgatggaaaaaaacctgatgacatcactatt
gatgtcaccattaacgaaagtataagtcatagtagaacagaagatgaaacaagaactcagattttgag
catcaagaaagttacctctgaggatctcaagcgcagctatgtctgtcatgctagaagtgccaaaggcg
aagttgccaaagcagccaaggtgaagcagaaaggtaatagatgcggtcagtgatgaatctctcagctc
caaattaacattgtggtgaataaggacaaaaggagagattgagaacaagagagctccagcacctagcc
cgacggcatctaacccatagtaatgaatcaaacttaaatgaaaaatatgaaagttttcatctatgtaa
gatactcaaaatattgtttctgatattgttagtaccgtaatgcccaaatgtagctaaaaaaatcgacg
tgagtacagtgagacacaattttgtgtctgtacaattatgaaaaattaaaaacaaagaaaatattcaa
agctaccaaagatagaaaaaactggtagagccacatattgttggtgaattattaagacccttttaaaa
atcattcatggtagagtttaagagtcataaaaaagattgcatcatctgacctaagactttcggaattt
ttcctgaacaaataacagaaagggaattatataccttttaatattattagaagcattatctgtagttg
taaaacattattaatagcagccatccaattgtatgcaactaattaaggtattgaatgtttattttcca
aaaatgcataattataatattatttaaacactatgtatcaatatttaagcaggtttataatatacca
gcagccacaattgctaaaatgaaaatcatttaaattatgattttaaatggtataaacatgatttctat
gttgatagtactatattattctacaataaatggaaattataaagccttcttgtcagaagtgctgctcc
taaaaaaaaaaaaaaaaaaaaa.

IL-1RAP, transcript variant 2, is encoded by the following amino acid sequence (NCBI Accession No. NM_134470 and SEQ ID NO: 27):

MTLLWCVVSLYFYGILQSDASERCDDWGLDTMRQIQVFEDEPARIKCPLFEHFLKFN
YSTAHSAGLTLIWYWTRQDRDLEEPINFRLPENRISKEKDVLWFRPTLLNDTGNYTC
MLRNTTYCSKVAFPLEVVQKDSCFNSPMKLPVHKLYIEYGIQRITCPNVDGYFPSSVK
PTITWYMGCYKIQNFNNVIPEGMNLSFLIALISNNGNYTCVVTYPENGRTFHLTRTLT
VKVVGSPKNAVPPVIHSPNDHVVYEKEPGEELLIPCTVYFSFLMDSRNEVWWTIDGK
KPDDITIDVTINESISHSRTEDETRTQILSIKKVTSEDLKRSYVCHARSAKGEVAKAAK
VKQKGNRCGQ.

Interleukin-1 Receptor Associated Kinase 1 (IRAK1):

The invention also comprises compositions and methods to inhibit the activity of human IRAK1, defined as the ability of this protein to bind an IL-1 receptor following ligation of this receptor with IL-1, as well as to transduce downstream signals leading to an inflammatory response. Compositions that comprise an inhibitor of IRAK1 antagonize downstream signaling from an IL-1 receptor. The composition comprises a polynucleotide, a polypeptide, an antibody, a compound, or a small molecule with means to inhibit the transcription, transcript stability, translation, modification, localization, secretion, or function of a polynucleotide or polypeptide encoding IRAK1. The inhibitory polynucleotide or polypeptide composition binds to one or more region(s) of IRAK1, and associated isoforms, comprised by SEQ ID NO: 28-33.

IRAK1, transcript variant 1, is encoded by the following mRNA sequence (NCBI Accession No. NM_001569 and SEQ ID NO: 28):

cgcggacccggccggcccaggcccgcgcccgccgcggccctgagaggccccggcaggtcccggcccgg
cggcggcagcc**ATG**gccgggggccgggcccgggggagcccgcagcccccggcgcccagcacttcttg
tacgaggtgccgccctgggtcatgtgccgcttctacaaagtgatggacgccctggagcccgccgactg
gtgccagttcgccgccctgatcgtgcgcgaccagaccgagctgcggctgtgcgagcgctccgggcagc
gcacggccagcgtcctgtggccctggatcaaccgcaacgcccgtgtggccgacctcgtgcacatcctc
acgcacctgcagctgctccgtgcgcgggacatcatcacagcctggcaccctcccgccccgcttccgtc
cccaggcaccactgccccgaggcccagcagcatccctgcacccgccgaggccgaggcctggagccccc
ggaagttgccatcctcagcctccaccttcctctccccagcttttccaggctcccagacccattcaggg
cctgagctcggcctggtcccaagccctgcttccctgtggcctccaccgccatctccagccccttcttc
taccaagccaggcccagagagctcagtgtccctcctgcagggagcccgcccctttccgttttgctggc
ccctctgtgagatttcccggggcacccacaacttctcggaggagctcaagatcggggagggtggcttt
gggtgcgtgtaccgggcggtgatgaggaacacggtgtatgctgtgaagaggctgaaggagaacgctga
cctggagtggactgcagtgaagcagagcttcctgaccgaggtggagcagctgtccaggtttcgtcacc
caaacattgtggactttgctggctactgtgctcagaacggcttctactgcctggtgtacggcttcctg
cccaacggctccctggaggaccgtctccactgccagacccaggcctgcccacctctctcctggcctca
gcgactggacatccttctgggtacagcccgggcaattcagtttctacatcaggacagccccagcctca
tccatggagacatcaagagttccaacgtccttctggatgagaggctgacacccaagctgggagacttt
ggcctggcccggttcagccgctttgccgggtccagccccagccagagcagcatggtggcccggacaca
gacagtgcggggcaccctggcctacctgcccgaggagtacatcaagacgggaaggctggctgtggaca
cggacaccttcagctttggggtggtagtgctagagaccttggctggtcagagggctgtgaagacgcac
ggtgccaggaccaagtatctgaaagacctggtggaagaggaggctgaggaggctggagtggctttgag

aagcacccagagcacactgcaagcaggtctggctgcagatgcctgggctgctcccatcgccatgcaga
tctacaagaagcacctggaccccaggcccgggccctgcccacctgagctgggcctgggcctgggccag
ctggcctgctgctgcctgcaccgccgggccaaaaggaggcctcctatgacccaggtgtacgagaggct
agagaagctgcaggcagtggtggcgggggtgcccgggcattcggaggccgccagctgcatccccccctt
ccccgcaggagaactcctacgtgtccagcactggcagagcccacagtggggctgctccatggcagccc
ctggcagcgccatcaggagccagtgcccaggcagcagagcagctgcagagaggccccaaccagcccgt
ggagagtgacgagagcctaggcggcctctctgctgccctgcgctcctggcacttgactccaagctgcc
ctctggacccagcacccctcagggaggccggctgtcctcaggggacacggcaggagaatcgagctgg
gggagtggcccaggatcccggcccacagccgtggaaggactggcccttggcagctctgcatcatcgtc
gtcagagccaccgcagattatcatcaaccctgcccgacagaagatggtccagaagctggccctgtacg
aggatggggccctggacagcctgcagctgctgtcgtccagctccctcccaggcttgggcctggaacag
gacaggcaggggcccgaagaaagtgatgaatttcagagctgatgtgttcacctgggcagatcccccaa
atccggaagtcaaagttctcatggtcagaagttctcatggtgcacgagtcctcagcactctgccggca
gtgggggtgggggcccatgcccgcgggggagagaaggaggtggccctgctgttctaggctctgtgggc
ataggcaggcagagtggaaccctgcctccatgccagcatctgggggcaaggaaggctggcatcatcca
gtgaggaggctggcgcatgttgggaggctgctggctgcacagacccgtgaggggaggagaggggctgc
tgtgcaggggtgtggagtagggagctggctcccctgagagccatgcagggcgtctgcagcccaggcct
ctggcagcagctctttgcccatctctttggacagtggccaccctgcacaatggggccgacgaggccta
gggccctcctacctgcttacaatttggaaaagtgtggccgggtgcggtggctcacgcctgtaatccca
gcactttgggaggccaaggcaggaggatcgctggagcccagtaggtcaagaccagccagggcaacatg
atgagaccctgtctctgccaaaaaatttttaaactattagcctggcgtggtagcgcacgcctgtggt
cccagctgctggggaggctgaagtaggaggatcatttatgcttgggaggtcgaggctgcagtgagtca
tgattgtatgactgcactccagcctgggtgacagagcaagaccctgtttcaaaaagaaaaaccctggg
aaaagtgaagtatggctgtaagtctcatggttcagtcctagcaagaagcgagaattctgagatcctcc
agaaagtcgagcagcacccacctccaacctcgggccagtgtcttcaggctttactggggacctgcgag
ctggcctaatgtggtggcctgcaagccaggccatccctgggcgccacagacgagctccgagccaggtc
aggcttcggaggccacaagctcagcctcaggcccaggcactgattgtggcagaggggccactacccaa
ggtctagctaggcccaagacctagttacccagacagtgagaagcccctggaaggcagaaaagttggga
gcatggcagacagggaagggaaacattttcagggaaaagacatgtatcacatgtcttcagaagcaagt
caggtttcatgtaaccgagtgtcctcttgcgtgtccaaaagtagcccagggctgtagcacaggcttca
cagtgattttgtgttcagccgtgagtcacactacatgcccccgtgaagctgggcattggtgacgtcca
ggttgtccttgagtaataaaaacgtatgttgcaataaaaaaaaaaaaaaaaa.

IRAK1, transcript variant 1, is encoded by the following amino acid sequence (NCBI Accession No. NM_001569 and SEQ ID NO: 29):

MAGGPGPGEPAAPGAQHFLYEVPPWVMCRFYKVMDALEPADWCQFAALIVRDQTE
LRLCERSGQRTASVLWPWINRNARVADLVHILTHLQLLRARDIITAWHPPAPLPSPGT
TAPRPSSIPAPAEAEAWSPRKLPSSASTFLSPAFPGSQTHSGPELGLVPSPASLWPPPPS
PAPSSTKPGPESSVSLLQGARPFPFCWPLCEISRGTHNFSEELKIGEGGFGCVYRAVMR
NTVYAVKRLKENADLEWTAVKQSFLTEVEQLSRFRHPNIVDFAGYCAQNGFYCLVY
GFLPNGSLEDRLHCQTQACPPLSWPQRLDILLGTARAIQFLHQDSPSLIHGDIKSSNVL
LDERLTPKLGDFGLARFSRFAGSSPSQSSMVARTQTVRGTLAYLPEEYIKTGRLAVDT
DTFSFGVVVLETLAGQRAVKTHGARTKYLKDLVEEEAEEAGVALRSTQSTLQAGLA
ADAWAAPIAMQIYKKHLDPRPGPCPPELGLGLGQLACCCLHRRAKRRPPMTQVYER
LEKLQAVVAGVPGHSEAASCIPPSPQENSYVSSTGRAHSGAAPWQPLAAPSGASAQA
AEQLQRGPNQPVESDESLGGLSAALRSWHLTPSCPLDPAPLREAGCPQGDTAGESSW
GSGPGSRPTAVEGLALGSSASSSSEPPQIIINPARQKMVQKLALYEDGALDSLQLLSSS
SLPGLGLEQDRQGPEESDEFQS.

IRAK1, transcript variant 2, is encoded by the following mRNA sequence (NCBI Accession No. NM_001025242 and SEQ ID NO: 30):

cgcggacccggccggcccaggcccgcgcccgccgcggccctgagaggccccggcaggtcccggcccgg
cggcggcagcc**ATG**gccgggggccgggcccgggggagcccgcagcccccggcgcccagcacttcttg
tacgaggtgccgccctgggtcatgtgccgcttctacaaagtgatggacgccctggagcccgccgactg
gtgccagttcgccgccctgatcgtgcgcgaccagaccgagctgcggctgtgcgagcgctccgggcagc
gcacggccagcgtcctgtggccctggatcaaccgcaacgcccgtgtggccgacctcgtgcacatcctc
acgcacctgcagctgctccgtgcgcgggacatcatcacagcctggcaccctcccgccccgcttccgtc
ccaggcaccactgccccgaggcccagcagcatccctgcacccgccgaggccgaggcctggagccccc
ggaagttgccatcctcagcctccaccttcctctccccagcttttccaggctcccagacccattcaggg
cctgagctcggcctggtcccaagccctgcttccctgtggcctccaccgccatctccagccccttcttc
taccaagccaggcccagagagctcagtgtccctcctgcagggagcccgcccctttccgttttgctggc
ccctctgtgagatttcccggggcacccacaacttctcggaggagctcaagatcggggagggtggcttt
gggtgcgtgtaccgggcggtgatgaggaacacggtgtatgctgtgaagaggctgaaggagaacgctga
cctggagtggactgcagtgaagcagagcttcctgaccgaggtggagcagctgtccaggtttcgtcacc
caaacattgtggactttgctggctactgtgctcagaacggcttctactgcctggtgtacggcttcctg
cccaacggctccctggaggaccgtctccactgccagacccaggcctgcccacctctctcctggcctca
gcgactggacatccttctgggtacagcccgggcaattcagtttctacatcaggacagccccagcctca
tccatggagacatcaagagttccaacgtccttctggatgagaggctgacacccaagctgggagacttt
ggcctggcccggttcagccgctttgccgggtccagccccagccagagcagcatggtggcccggacaca
gacagtgcggggcaccctggcctacctgcccgaggagtacatcaagacgggaaggctggctgtggaca
cggacaccttcagctttggggtggtagtgctagagaccttggctggtcagagggctgtgaagacgcac
ggtgccaggaccaagtatctgaaagacctggtggaagaggaggctgaggaggctggagtggctttgag
aagcacccagagcacactgcaagcaggtctggctgcagatgcctgggctgctcccatcgccatgcaga
tctacaagaagcacctggaccccaggcccgggccctgcccacctgagctgggcctgggcctgggccag
ctggcctgctgctgcctgcaccgccgggccaaaaggaggcctcctatgacccaggagaactcctacgt
gtccagcactggcagagcccacagtggggctgctccatggcagcccctggcagcgccatcaggagcca
gtgcccaggcagcagagcagctgcagagaggccccaaccagcccgtggagagtgacgagagcctaggc
ggcctctctgctgccctgcgctcctggcacttgactccaagctgccctctggacccagcacccctcag
ggaggccggctgtcctcaggggacacggcaggagaatcgagctgggggagtggcccaggatcccggc
ccacagccgtggaaggactggcccttggcagctctgcatcatcgtcgtcagagccaccgcagattatc
atcaaccctgcccgacagaagatggtccagaagctggccctgtacgaggatggggccctggacagcct
gcagctgctgtcgtccagctccctcccaggcttgggcctggaacaggacaggcaggggcccgaagaaa
gtgatgaatttcagagctgatgtgttcacctgggcagatcccccaaatccggaagtcaaagttctcat
ggtcagaagttctcatggtgcacgagtcctcagcactctgccggcagtgggggtgggggcccatgccc
gcgggggagagaaggaggtggccctgctgttctaggctctgtgggcataggcaggcagagtggaaccc
tgcctccatgccagcatctgggggcaaggaaggctggcatcatccagtgaggaggctggcgcatgttg
ggaggctgctggctgcacagacccgtgaggggaggagaggggctgctgtgcaggggtgtggagtaggg
agctggctcccctgagagccatgcagggcgtctgcagcccaggcctctggcagcagctctttgcccat
ctctttggacagtggccaccctgcacaatggggccgacgaggcctagggccctcctacctgcttacaa
tttggaaaagtgtggccgggtgcggtggctcacgcctgtaatcccagcactttgggaggccaaggcag
gaggatcgctggagcccagtaggtcaagaccagccagggcaacatgatgagaccctgtctctgccaaa
aaatttttaaactattagcctggcgtggtagcgcacgcctgtggtcccagctgctggggaggctgaa
gtaggaggatcatttatgcttgggaggtcgaggctgcagtgagtcatgattgtatgactgcactccag
cctgggtgacagagcaagaccctgtttcaaaaagaaaaaccctgggaaaagtgaagtatggctgtaag
tctcatggttcagtcctagcaagaagcgagaattctgagatcctccagaaagtcgagcagcacccacc
tccaacctcgggccagtgtcttcaggctttactggggacctgcgagctggcctaatgtggtggcctgc
aagccaggccatccctgggcgccacagacgagctccgagccaggtcaggcttcggaggccacaagctc
agcctcaggcccaggcactgattgtggcagaggggccactacccaaggtctagctaggcccaagacct
agttacccagacagtgagaagcccctggaaggcagaaaagttgggagcatggcagacagggaagggaa
acattttcagggaaaagacatgtatcacatgtcttcagaagcaagtcaggtttcatgtaaccgagtgt
cctcttgcgtgtccaaaagtagcccagggctgtagcacaggcttcacagtgattttgtgttcagccgt
gagtcacactacatgcccccgtgaagctgggcattggtgacgtccaggttgtccttgagtaataaaaa
cgtatgttgcaataaaaaaaaaaaaaaaaa.

IRAK1, transcript variant 2, is encoded by the following amino acid sequence (NCBI Accession No. NM_001025242 and SEQ ID NO: 31):

MAGGPGPGEPAAPGAQHFLYEVPPWVMCRFYKVMDALEPADWCQFAALIVRDQTE
LRLCERSGQRTASVLWPWINRNARVADLVHILTHLQLLRARDIITAWHPPAPLPSPGT
TAPRPSSIPAPAEAEAWSPRKLPSSASTFLSPAFPGSQTHSGPELGLVPSPASLWPPPPS
PAPSSTKPGPESSVSLLQGARPFPFCWPLCEISRGTHNFSEELKIGEGGFGCVYRAVMR
NTVYAVKRLKENADLEWTAVKQSFLTEVEQLSRFRHPNIVDFAGYCAQNGFYCLVY
GFLPNGSLEDRLHCQTQACPPLSWPQRLDILLGTARAIQFLHQDSPSLIHGDIKSSNVL
LDERLTPKLGDFGLARFSRFAGSSPSQSSMVARTQTVRGTLAYLPEEYIKTGRLAVDT
DTFSFGVVVLETLAGQRAVKTHGARTKYLKDLVEEEAEEAGVALRSTQSTLQAGLA
ADAWAAPIAMQIYKKHLDPRPGPCPPELGLGLGQLACCCLHRRAKRRPPMTQENSY
VSSTGRAHSGAAPWQPLAAPSGASAQAAEQLQRGPNQPVESDESLGGLSAALRSWH
LTPSCPLDPAPLREAGCPQGDTAGESSWGSGPGSRPTAVEGLALGSSASSSSEPPQIIIN
PARQKMVQKLALYEDGALDSLQLLSSSSLPGLGLEQDRQGPEESDEFQS.

IRAK1, transcript variant 3, is encoded by the following mRNA sequence (NCBI Accession No. NM_ 001025243 and SEQ ID NO: 32):

cgcggacccggccggcccaggcccgcgcccgccgcggccctgagaggccccggcaggtcccggcccgg
cggcggcagcc**ATG**gccgggggggccgggcccgggggagcccgcagcccccggcgcccagcacttcttg
tacgaggtgccgccctgggtcatgtgccgcttctacaaagtgatggacgccctggagcccgccgactg
gtgccagttcgccgccctgatcgtgcgcgaccagaccgagctgcggctgtgcgagcgctccgggcagc
gcacggccagcgtcctgtggccctggatcaaccgcaacgcccgtgtggccgacctcgtgcacatcctc
acgcacctgcagctgctccgtgcgcgggacatcatcacagcctggcaccctcccgccccgcttccgtc
cccaggcaccactgccccgaggcccagcagcatccctgcacccgccgaggccgaggcctggagccccc
ggaagttgccatcctcagcctccaccttcctctccccagcttttccaggctcccagacccattcaggg
cctgagctcggcctggtcccaagccctgcttccctgtggcctccaccgccatctccagccccttcttc
taccaagccaggcccagagagctcagtgtccctcctgcagggagcccgcccctttccgttttgctggc
ccctctgtgagatttcccggggcacccacaacttctcggaggagctcaagatcggggagggtggcttt
gggtgcgtgtaccgggcggtgatgaggaacacggtgtatgctgtgaagaggctgaaggagaacgctga
cctggagtggactgcagtgaagcagagcttcctgaccgaggtggagcagctgtccaggtttcgtcacc
caaacattgtggactttgctggctactgtgctcagaacggcttctactgcctggtgtacggcttcctg
cccaacggctccctggaggaccgtctccactgccagacccaggcctgcccacctctctcctggcctca
gcgactggacatccttctgggtacagcccgggcaattcagtttctacatcaggacagccccagcctca
tccatggagacatcaagagttccaacgtccttctggatgagaggctgacacccaagctgggagacttt
ggcctggcccggttcagccgctttgccgggtccagccccagccagagcagcatggtggcccggacaca
gacagtgcggggcaccctggcctacctgcccgaggagtacatcaagacgggaaggctggctgtggaca
cggacaccttcagctttggggtggtagtgctagagaccttggctggtcagagggctgtgaagacgcac
ggtgccaggaccaagtatctggtgtacgagaggctagagaagctgcaggcagtggtggcgggggtgcc
cgggcattcggaggccgccagctgcatccccccttccccgcaggagaactcctacgtgtccagcactg
gcagagcccacagtggggctgctccatggcagcccctggcagcgccatcaggagccagtgcccaggca
gcagagcagctgcagagaggccccaaccagcccgtggagagtgacgagagcctaggcggcctctctgc
tgccctgcgctcctggcacttgactccaagctgccctctggacccagcacccctcagggaggccggct
gtcctcaggggacacggcaggagaatcgagctgggggagtggcccaggatcccggcccacagccgtg
gaaggactggcccttggcagctctgcatcatcgtcgtcagagccaccgcagattatcatcaaccctgc
ccgacagaagatggtccagaagctggccctgtacgaggatggggccctggacagcctgcagctgctgt
cgtccagctccctcccaggcttgggcctggaacaggacaggcaggggcccgaagaaagtgatgaattt
cagagctgatgtgttcacctgggcagatccccaaatccggaagtcaaagttctcatggtcagaagtt
ctcatggtgcacgagtcctcagcactctgccggcagtgggggtgggggcccatgcccgcgggggagag
aaggaggtggccctgctgttctaggctctgtgggcataggcaggcagagtggaaccctgcctccatgc
cagcatctgggggcaaggaaggctggcatcatccagtgaggaggctggcgcatgttgggaggctgctg
gctgcacagacccgtgaggggaggagaggggctgctgtgcaggggtgtggagtagggagctggctccc
ctgagagccatgcagggcgtctgcagcccaggcctctggcagcagctctttgcccatctctttggaca
gtggccaccctgcacaatggggccgacgaggcctagggccctcctacctgcttacaatttggaaaagt
gtggccgggtgcggtggctcacgcctgtaatcccagcactttgggaggccaaggcaggaggatcgctg
gagcccagtaggtcaagaccagccagggcaacatgatgagaccctgtctctgccaaaaaatttttttaa

actattagcctggcgtggtagcgcacgcctgtggtcccagctgctggggaggctgaagtaggaggatc
atttatgcttgggaggtcgaggctgcagtgagtcatgattgtatgactgcactccagcctgggtgaca
gagcaagaccctgtttcaaaaagaaaaaccctgggaaaagtgaagtatggctgtaagtctcatggttc
agtcctagcaagaagcgagaattctgagatcctccagaaagtcgagcagcacccacctccaacctcgg
gccagtgtcttcaggctttactggggacctgcgagctggcctaatgtggtggcctgcaagccaggcca
tccctgggcgccacagacgagctccgagccaggtcaggcttcggaggccacaagctcagcctcaggcc
caggcactgattgtggcagaggggccactacccaaggtctagctaggcccaagacctagttacccaga
cagtgagaagcccctggaaggcagaaaagttgggagcatggcagacagggaagggaaacattttcagg
gaaaagacatgtatcacatgtcttcagaagcaagtcaggtttcatgtaaccgagtgtcctcttgcgtg
tccaaaagtagcccagggctgtagcacaggcttcacagtgattttgtgttcagccgtgagtcacacta
catgcccccgtgaagctgggcattggtgacgtccaggttgtccttgagtaataaaaacgtatgttgca
ataaaaaaaaaaaaaaaaaa.

IRAK1, transcript variant 3, is encoded by the following amino acid sequence (NCBI Accession No. NM_ 001025243 and SEQ ID NO: 33):

MAGGPGPGEPAAPGAQHFLYEVPPWVMCRFYKVMDALEPADWCQFAALIVRDQTE
LRLCERSGQRTASVLWPWINRNARVADLVHILTHLQLLRARDIITAWHPPAPLPSPGT
TAPRPSSIPAPAEAEAWSPRKLPSSASTFLSPAFPGSQTHSGPELGLVPSPASLWPPPPS
PAPSSTKPGPESSVSLLQGARPFPFCWPLCEISRGTHNFSEELKIGEGGFGCVYRAVMR
NTVYAVKRLKENADLEWTAVKQSFLTEVEQLSRFRHPNIVDFAGYCAQNGFYCLVY
GFLPNGSLEDRLHCQTQACPPLSWPQRLDILLGTARAIQFLHQDSPSLIHGDIKSSNVL
LDERLTPKLGDFGLARFSRFAGSSPSQSSMVARTQTVRGTLAYLPEEYIKTGRLAVDT
DTFSFGVVVLETLAGQRAVKTHGARTKYLVYERLEKLQAVVAGVPGHSEAASCIPPS
PQENSYVSSTGRAHSGAAPWQPLAAPSGASAQAAEQLQRGPNQPVESDESLGGLSA
ALRSWHLTPSCPLDPAPLREAGCPQGDTAGESSWGSGPGSRPTAVEGLALGSSASSSS
EPPQIIINPARQKMVQKLALYEDGALDSLQLLSSSSLPGLGLEQDRQGPEESDEFQS.

Silencing Expression with MicroRNAs

The present invention comprises compositions with means to inhibit the activity of IL-1α, IL-1b, IL-1R1, IL-1R2, IL-1Ra3, IL-1RAP, or IRAK1, by delivering microRNA (miRNA) molecules to an ocular or adnexal tissue with an appropriate pharmaceutical carrier. Compositions that comprise a miRNA targeted to either IL-1α, IL-1b, IL-1R1, IL-1R2, IL-1Ra3, IL-1RAP, or IRAK1 antagonize the function of IL-1R1. The composition comprises one or more miRNA(s) that bind to one or more regions of IL-1α, IL-1b, IL-1R1, IL-1R2, IL-1Ra3, IL-1RAP, or IRAK1. The following table contains exemplary miRNAs that have been shown to partially or completely silence the expression of human IL-1α or IL-1R1.

Table 1: Summary of miRNAs, their human target genes, nucleotide sequences, and their sequence identifier numbers.

Target Gene	miRNA	Polynucleotide sequence (5' to 3')	SEQ ID NO:
IL-1α	miR-30c	UGUAAACAUCCUACACUCUCAGC	34

IL-1α	miR-30b	UGUAAACAUCCUACACUCAGC	35
IL-1α	miR-30a-5p	UGUAAACAUCCUCGACUGGAAGC	36
IL-1α	miR-24	UGGCUCAGUUCAGCAGGAACAG	37
IL-1R1	miR-135b	UAUGGCUUUUCAUUCCUAUGUG	38
IL-1R1	miR-326	CCUCUGGGCCCUUCCUCCAG	39
IL-1R1	miR-184	UGGACGGAGAACUGAUAAGGGU	40
IL-1R1	miR-214	ACAGCAGGCACAGACAGGCAG	41
IL-1R1	miR-203	GUGAAAUGUUUAGGACCACUAG	42
IL-1R1	miR-331	GCCCCUGGGCCUAUCCUAGAA	43
IL-1R1	miR-205	UCCUUCAUUCCACCGGAGUCUG	44

IL-1 and IL-1R-Mediated Signaling

As used herein, the phrase "inhibit an activity of an inflammatory interleukin-1 cytokine" is meant to describe the inhibition, prevention, diminution, reduction, decrease, repression, or interruption intracellular signaling initiated, communicated, or transduced from an IL-1 receptor. In one aspect of the invention, inhibition, prevention, diminution, reduction, decreases, repression, or interruption of intracellular signaling initiated, communicated, or transduced from an IL-1 receptor is achieved by preventing or decreasing binding of an IL-1 cytokine to an IL-1R. Alternatively, or in addition, transduction of intracellular signaling from an IL-1R is prevented by removing, silencing, or mutating a downstream effector or target within a signaling cascade. The expression and/or function or activity of downstream effectors and/or targets are removed (*e.g.*, deleted, knocked-out, sequestered, denatured, degraded, etc.), silenced (degraded, transcriptionally or translationally repressed), or mutated (nucleotide or amino acid sequence encoding the active product is altered to encode a non-functional product) by genetic modification or administration of a therapeutic compound.

Exemplary downstream effectors and/or targets include, but are not limited to, one or more isoforms or homologs of an IL-1 (interleukin 1), an IL-1α (interleukin 1 alpha), an IL-1β (interleukin 1 beta), an IL-1R (interleukin 1 receptor, type I), an IL-1Ra (IIL-1R antagonist), an IL-1RAcP (IL-1R accessory protein), a TOLLIP (TOLL interacting protein), an IRAK1 (IL-1R associated kinase 1), an IRAK2 (IL-1R associated kinase 2), an IRAK 3 (IL-1R associated kinase 3), a MYD88 (myeloid differentiation primary response gene 88), an ECSIT (evolutionarily conserved signaling intermediate in Toll pathways), a TRAF6 (TNF-receptor associated factor 6), a MEKK1 (MAP ERK kinase kinase 1), a TAB1 (TAK1 binding protein 1), a TAK1 (transforming growth factor b activated kinase 1), a NIK (NFkB Inducing Kinase), a RKIP (Raf kinase inhibitor protein), a MEK3 (Mitogen-Activated Protein Kinase Kinase 3; MEK3 or MKK3), a MEK6 (Mitogen-Activated Protein Kinase Kinase 6; MEK6 or MKK6), a MAPK14 (mitogen activated protein kinase 14), a MAPK8 (mitogen

activated protein kinase 8), a MEKK1 (mitogen activated protein kinase kinase kinase 1), a MAP3K14 (mitogen activated protein kinase kinase kinase 14), a MEKK7 (mitogen activated protein kinase kinase kinase 7 or MKK7), a MAP3K7IP1 (mitogen activated protein kinase kinase kinase 7 interacting protein 1), a JNK (Jun N-terminal kinase), p38 (also known as p38 MAPK or p38 mitogen activated protein kinase), cJUN (jun oncogene), AP-1 (activator protein 1; transcription factor), IL-6 (interleukin 6, also known as interferon beta 2), TNFα (tumor necrosis factor-alpha), a TNF (tumor necrosis factor superfamily member), an IFNα (interferon alpha, interferon alpha 1), an IFNβ (interferon beta, interferon beta 1), a TGFβ1 (transforming growth factor beta 1), a TGFβ2 (transforming growth factor beta 2), a TGFβ3 (transforming growth factor beta 3), an IKKα (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase alpha), an IKKβ (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta), a IκBα (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha), a Chuk (conserved helix-loop-helix ubiquitous kinase), and a NFκB (nuclear factor of kappa light polypeptide gene enhancer in B-cells 1; also known as p105). Additional signaling molecules and relationships are defined by O'Neill, L. A. J. and Greene, C. 1998. Journal of Leukocyte Biology. 63: 650-657.

The inhibition of an activity of an interleukin-1 cytokine is determined by sampling the cornea and determining the abundance of a polynucleotide or polypeptide which encodes for component of an IL-1R signaling cascade. An increase or decrease in the abundance of a polynucleotide or polypeptide which encodes for component of an IL-1R signaling cascade following administration of a therapeutic composition of the invention compared to the abundance of the component of an IL-1R signaling cascade prior to the administration indicates inhibition of an activity of an inflammatory interleukin-1 cytokine.

Specifically, Figure 5 shows the functional interrelationships between components of two exemplary signaling cascades. The arrows between components in this figure indicate that the component preceding the arrow activates the component following the arrow. Conversely, the blunted lines indicated that the component preceding the blunted line inhibits the activity or function of the component following the blunted line.

Briefly, the IL-1R, type I, binds IL-1β, however, IL-1R requires the IL-1 receptor accessory protein (IL-1RAcP) to transduce a signal. IL-1 binding causes activation of two kinases, IRAK-1 and IRAK-2, associated with the IL-1 receptor complex. IRAK-1 (IL-1 Receptor Associated Kinase) activates and recruits TRAF6 to the IL-1 receptor complex. TRAF6 activates two pathways, one leading to NF-kB activation and another leading to c-jun

activation. The TRAF associated protein ECSIT leads to c-Jun activation through the Map kinase/JNK signaling system. TRAF6 also signals through the TAB1/TAK1 kinases to trigger the degradation of I-kB, and activation of NF-kB.

For instance, in certain embodiments of the invention, a decrease in the abundance or absence of the processed form of MEKK1, a decrease in the abundance or absence of phosphorylated IκBα, a decrease in the abundance or absence of phosphorylated c-JUN, a decrease in the abundance or absence of ICAM-1, or a decrease in the abundance or absence of IL-6, TNFα, IFNα, IFNβ, TGFβ is indicative of inhibition of an interleukin-1 cytokine. Similarly, a decrease or absence of activity or function of any of the above-listed components is indicative of inhibition of an interleukin-1 cytokine.

Pharmaceutically-Appropriate Carriers

Exemplary compounds incorporated to facilitate and expedite local delivery of topical compositions into ocular or adnexal tissues include, but are not limited to, alcohol (ethanol, propanol, and nonanol), fatty alcohol (lauryl alcohol), fatty acid (valeric acid, caproic acid and capric acid), fatty acid ester (isopropyl myristate and isopropyl n-hexanoate), alkyl ester (ethyl acetate and butyl acetate), polyol (propylene glycol, propanedione and hexanetriol), sulfoxide (dimethylsulfoxide and decylmethylsulfoxide), amide (urea, dimethylacetamide and pyrrolidone derivatives), surfactant (sodium lauryl sulfate, cetyltrimethylammonium bromide, polaxamers, spans, tweens, bile salts and lecithin), terpene (d-limonene, alpha-terpeneol, 1,8-cineole and menthone), and alkanone (N-heptane and N-nonane). Moreover, topically-administered compositions comprise surface adhesion molecule modulating agents including, but not limited to, a cadherin antagonist, a selectin antagonist, and an integrin antagonist.

Optionally, the composition further contains a compound selected from the group consisting of a physiological acceptable salt, poloxamer analogs with carbopol, carbopol/hydroxypropyl methyl cellulose (HPMC), carbopol-methyl cellulose, N-acetyl cysteine, carboxymethylcellulose (CMC), hyaluronic acid, cyclodextrin, and petroleum.

EXAMPLES

Example 1: Effect of IL-1 Blockade on Central Nerve Regeneration in Epithelial Disease

It was observed that subjects with the most severe clinical signs of dry eye reported feeling surprising improvement after administration of IL-1 blockade. Upon further investigation, patients with severe dry eye were found to also suffer after administration of IL-1 blockade corneal nerve damage or even loss of nerve function. To better elucidate the mechanism of this unexpected improvement following treatment, the contribution of nerve

damage and function to the normal and pathological processes of tear production and dry eye was investigated.

To examine the role of IL-1 blockade in corneal nerve homeostasis, regeneration of the corneal subbasal nerve plexus and terminal epithelial branches after epithelial debridement was measured. Mice were anesthetized, and a 2-mm circular corneal epithelial defect was made in one eye of each anesthetized mouse using a scalpel blade. One group of mice (n=5) was treated with topical eye drop of IL-1Ra 2.5% mixed with carboxymethylcellulose 1% , 3 times a day for 7 days. The control group (n=5) was treated using vehicle (carboxymethylcellulose 1%), 3 times a day for 7 days. After 7 days, animals were euthanized, and corneas were removed and fixed in 4% Para formaldehyde for 40 minutes at room temperature. Corneas were washed with PBS. Permeabilization and blocking was achieved with 2-hour incubation in 2% BSA in PBS and 0.2% Triton X-100. Corneas were incubated with rabbit anti-mouse ß III tubulin primary antibody at a dilution of 1:200 for 16 hours at 4°. After three washes in PBS corneas were incubated in goat anti-rabbit secondary antibody conjugated to rhodamine at a dilution of 1:200 for 2 hours at room temperature. The corneas were coverslipped with mounting medium and imaged. The corneas were photographed at the level of the subbasal nerve plexus and terminal branching in cornea paracentral regions in the area of the wound (Figure 1). For the treated eye, nerve density at the level of terminal branching was normalized to the contralateral normal cornea. The results of this experiment showed that in the IL-1Ra-treated group, the percent density of regenerated nerve at the level of basal epithelial cell was 80% compared to 15% in the vehicle-treated group.

In a clinical human study in patients with dry eye-associated ocular surface disease using in-vivo confocal microscopy (Confoscan 4; Nidek Technologies), corneal nerve morphology at the level of subbasal corneal nerve was assessed before and after one-month treatment with topical IL-1Ra 2.5% three times a day (Figure 2). After the treatment with IL-1 blockade in a total of 6 patients, the sum of the length of the nerves per image (nerve fiber density) was increased by 25% compared to baseline. The improvement in corneal nerve density was correlated with the reduction of signs and symptoms of dry eye in these patients.

IL-1 blockade, therefore, helps the epithelium improve its maintenance of corneal health by increasing nerve regeneration, which in turn breaks the vicious cycle of epithelial disease and nerve damage. Thus, IL-1 blockade can be used in all ophthalmologic conditions that affect the corneal epithelial health, including all forms of dry eye syndrome, all form of ocular surface diseases, corneal surgeries such as refractive surgeries (PRK, LASEK, Epi-

LASIK, LASIK), corneal transplantation, epithelial debridement, ocular surface reconstruction, herpetic keratitis, neurotrophic keratitis, exposure keratopathy, diabetes mellitus, trigeminal nerve damage. Non-ophthalmic applications of IL-1 blockade would be all forms of peripheral neuropathy including diabetic peripheral neuropathy.

Example 2: Effect of IL-1 Blockade on Dry-Eye Induced Lymphangiogenesis

Corneal angiogenesis is involved in the pathogenesis of adaptive immunity to corneal antigens and in inducing ocular surface disease. Lymphatic vessels are crucial for migration of resident antigen presenting cells to the draining lymph nodes and induction of adaptive immunity, but there is no information about the role of lymphangiogenesis in dry-eye associated ocular surface disease. In a mouse model of dry eye, it was determined whether IL-1 blockade can reduce dry-eye induced lymphangiogenesis. Dry eye was induced in female C57BL/6 mice (n=10) by exposure to the controlled environment chamber and to systemic scopolamine. After 2 days, one group of mice (n=5) received topical IL-1Ra 2.5% mixed with carboxymethylcellulose 1% three times a day, and the second group received only the vehicle (carboxymethylcellulose 1%). After 5 days of treatment, animals were euthanized, and corneas were removed and fixed in 4% Para formaldehyde for 40 minutes at room temperature. Immunohistochemical staining for lymphatic vessels and blood vessels was performed on corneal flat mounts. Immunohistochemical staining against LYVE-1 (lymphatic endothelium–specific hyaluronic acid receptor) was performed with purified antibody followed by rhodamine conjugated secondary antibody. Immunohistochemical staining was also performed with FITC-conjugated CD31. To quantify the level of blood vessel formation and lymphatic vessel formation, low magnification (2×) micrographs were captured and the area covered by lymph neovessels were calculated and expressed as % of total corneal area. IL-1Ra-treated corneas showed on average 60% less lymphangiogenesis activity compared to vehicle-treated corneas. In addition, blockade of IL-1 led to the immune cells having a lower level of maturity, which renders them less able to sensitize T cells.

The results of this experiment show that the compounds having the inhibitory activity against IL-1 on prevention of dry-eye associated lymphangiogenesis are useful to minimize the induction of adaptive immunity and autoimmunity in dry-eye associated ocular surface disease.

Example 3: Concentration of Topical IL-1Ra

With respect to effects of IL-1 blockade on dry eye disease, different concentrations (1%, 2.5%, and 5%) of topical IL-1Ra mixed with carboxymethylcellulose 1% were tested in a mouse model of dry eye. Dry eye was induced in female C57BL/6 mice (n=20) by

exposure to the controlled environment chamber and to systemic scopolamine. After 2 days, mice were divided in 5 groups. The first, second, and third groups of mice (4 mice in each group) received topical IL-1Ra 5%, 2.5%, and 1% respectively, mixed with carboxymethylcellulose 1% in frequency of 3 times a day; the fourth group (n=4) received vehicle (carboxymethylcellulose 1%) in frequency of 3 times a day; and the fifth group (n=4) left untreated. After 5 days of treatment, corneal fluorescein staining was performed by applying 0.5 μL of 1% fluorescein by micropipette into the inferior conjunctival sac of the mouse eye. The cornea was examined with a slit lamp biomicroscope in cobalt blue light 3 minutes after fluorescein instillation. Punctuate staining was recorded in a masked fashion with a standardized (National Eye Institute) grading system of 0 to 3 for each of the five areas in which the corneal surface was divided. This experiment showed that all concentrations of IL-1Ra (1%, 2.5%, and 5%) can decrease the corneal fluorescein staining score, however, percent reduction of corneal fluorescein staining was modestly higher in the group that received topical IL-1Ra with concentration of 5%.

Example 4: Formulation of Topical IL-1Ra

With respect to effects of IL-1 blockade on dry eye disease, IL-1Ra 5% mixed with different vehicles was tested in a mouse model of dry eye. Dry eye was induced in female C57BL/6 mice (n=20) by exposure to the controlled environment chamber and to systemic scopolamine. After 2 days, mice were divided in 4 groups. The first group of mice (n=5) received topical IL-1Ra 5% mixed with carboxymethylcellulose 1% in frequency of 3 times a day; the second group (n=5) received topical IL-1Ra 5% mixed with N-acetyl cysteine 10% in frequency of 3 times a day; the third group (n=5) received topical IL-1Ra 5% mixed with hypromellose (hydroxypropyl methylcellulose) 0.3 % and glutathione 0.3 mmol/L; and the fourth group (n=5) left untreated. After 5 days of treatment, corneal fluorescein staining was performed by applying 0.5 μL of 1% fluorescein by micropipette into the inferior conjunctival sac of the mouse eye. The cornea was examined with a slit lamp biomicroscope in cobalt blue light 3 minutes after fluorescein instillation. Punctuate staining was recorded in a masked fashion with a standardized (National Eye Institute) grading system of 0 to 3 for each of the five areas in which the corneal surface was divided. This experiment showed that percent reduction of corneal fluorescein staining was significantly higher in the group received topical IL-1Ra 5% mixed with N-acetyl cysteine 10% and the group received topical IL-1Ra 5% mixed with carboxymethylcellulose 1%.

Example 5: Minimization or prevention of corneal nerve degeneration

To examine the role of IL-1 blockade in corneal nerve homeostasis, minimization and prevention of nerve degeneration of the corneal subbasal nerve plexus and terminal epithelial branches was measured. One group of mice (n=5) was treated with topical eye drop of IL-1Ra , 2.5% mixed with carboxymethylcellulose 1% , 3 times a day for 7 days. The control group (n=5) was treated using vehicle (carboxymethylcellulose 1%), 3 times a day for 7 days. Mice were then anesthetized, and a 2-mm circular corneal epithelial defect was made in one eye of each anesthetized mouse using a scalpel blade. After 7 days, animals were euthanized, and corneas were removed and fixed in 4% Para formaldehyde for 40 minutes at room temperature. Corneas were washed with PBS. Permeabilization and blocking was achieved with 2-hour incubation in 2% BSA in PBS and 0.2% Triton X-100. Corneas were incubated with rabbit anti-mouse ß III tubulin primary antibody at a dilution of 1:200 for 16 hours at 4°. After three washes in PBS corneas were incubated in goat anti-rabbit secondary antibody conjugated to rhodamine at a dilution of 1:200 for 2 hours at room temperature. The corneas were coverslipped with mounting medium and imaged. The corneas are photographed at the level of the subbasal nerve plexus and terminal branching in cornea paracentral regions in the area of the wound. For the treated eye, nerve density at the level of terminal branching is normalized to the contralateral normal cornea. The results of this experiment show that that in the IL-1Ra-treated group, the percent density of degenerated nerve at the level of basal epithelial cell was decreased compared to the vehicle-treated group.

IL-1 blockade, therefore, can help the epithelium improve its maintenance of corneal health by minimizing or preventing nerve degeneration which in turn can break the vicious cycle of epithelial disease and nerve damage. Thus, IL-1 blockade can be used in all ophthalmologic conditions that affect the corneal epithelial health including all forms of dry eye syndrome, all form of ocular surface diseases, corneal surgeries such as refractive surgeries (PRK, LASEK, Epi-LASIK, LASIK), corneal transplantation, epithelial debridement, ocular surface reconstruction, herpetic keratitis, neurotrophic keratitis, exposure keratopathy, diabetes mellitus, trigeminal nerve damage. Non-ophthalmic applications of IL-1 blockade would be all forms of peripheral neuropathy including diabetic peripheral neuropathy.

Example 6: IL-1 and IL-17 blockade provides unexpected protection of corneal nerves

As described in WO/2009/089036, which is incorporated herein by reference, the method comprises administration of a compound that inhibits binding of an inflammatory IL-17 cytokine to the IL- 17 receptor complex.

A method for regenerating corneal nerves is also carried out by locally administering to an eye of a subject a composition comprising a polynucleotide, a polypeptide, an antibody, a compound, or a small molecule that inhibits or modifies the transcription, transcript stability, translation, modification, localization, secretion, or function of a polynucleotide or polypeptide encoding an inflammatory interleukin-17 cytokine or any component of the IL-17 receptor complex.

The composition may comprise a neutralizing or function-blocking antibody against IL- 17 and/or a receptor complex. The neutralizing or function-blocking antibody against IL-17 may be a reformulated or humanized derivative of or bind to the epitope of human IL- 17 affinity purified polyclonal antibody (Catalog # AF-317-NA, R&D Systems), human IL- 17 allophycocyanin monoclonal antibody (clone 41802)(Catalog # IC3171A, R&D Systems), human IL- 17 biotinylated affinity purified polyclonal antibody (Catalog # BAF317, R&D Systems), human IL- 17 monoclonal antibody (clone 41802)(Catalog # MAB3171 , R&D Systems), human IL- 17 monoclonal antibody (clone 41809)(Catalog # MAB317, R&D Systems), human IL- 17 phycoerythrin monoclonal antibody (clone 41802)(Catalog # IC3171P, R&D Systems), mouse IL- 17 affinity purified polyclonal antibody (Catalog # AF-421 -NA, R&D Systems), mouse IL- 17 biotinylated affinity purified polyclonal antibody (Catalog # BAF421, R&D Systems), mouse IL- 17 monoclonal antibody (clone 50101)(Catalog # MAB721 , R&D Systems), or mouse IL- 17 monoclonal antibody (clone 50104)(Catalog # MAB421 , R&D Systems). Preferably, the neutralizing or function-blocking antibody against IL- 17 may be a reformulated or humanized derivative of or bind to the epitope of monoclonal anti-human IL- 17 antibody, (Clone: 41809, Catalog # MAB317, R&D Systems), anti-human IL- 17 antibody, polyclonal raised in Goat, (Catalog # AF-317-NA, R&D Systems), or recombinant human IL- 17 RTFc chimera (Catalog # 177-IR, R&D Systems).

By "reformulate" is meant altering the composition to make it suitable for topical administration, subconjunctival administration, episcleral space administration, subcutaneous administration, or intraductal administration. Preferred formulations are in the form of a solid, a paste, an ointment, a gel, a liquid, an aerosol, a mist, a polymer, a contact lens, a film, an emulsion, or a suspension. In one aspect, the formulations are administered topically, *e.g.*, the composition is delivered and directly contacts the eye. Optionally, the compositions are administered with a pharmaceutically acceptable liquid carrier, *e.g.*, a liquid carrier, which is aqueous or partly aqueous. Alternatively, the compositions are associated with a liposome (*e.g.*, a cationic or anionic liposome).

The neutralizing or function-blocking antibody against an IL-17 receptor (I1-17R) may be a reformulated or humanized derivative of or bind to the epitope of human IL- 17R affinity purified polyclonal antibody (Catalog # AF 177, R&D Systems), human IL- 17R allophycocyanin monoclonal antibody (clone 133617)(Catalog # FAB177A, R&D Systems), human IL- 17R biotinylated affinity purified polyclonal antibody (Catalog # BAF 177, R&D Systems), human IL-17R fluorescein monoclonal antibody (clone 133617) (Catalog # FAB177F, R&D Systems), human IL-17R monoclonal antibody (clone 133617)(Catalog # MAB 177, R&D Systems), human IL- 17R monoclonal antibody (clone 133621)(Catalog # MAB 1771 , R&D Systems), human IL- 17R phycoerythrin monoclonal antibody (clone 133617)(Catalog #FAB 177P, R&D Systems), mouse IL- 17R affinity purified polyclonal antibody (Catalog # AF448A, R&D Systems), mouse IL- 17R biotinylated affinity purified polyclonal antibody (Catalog # BAF448, R&D Systems), or mouse IL- 17R monoclonal antibody (clone 105828)(Catalog # MAB448, R&D Systems).

The neutralizing or function-blocking antibody against an IL- 17 may be a reformulated or humanized derivative of, or bind to the epitope of, one or more mouse anti-IL-17A (SKU #s including but not limited to, 7172, 7173, 7175, 7177, 8171, 7371 , 7971, and 7370, eBioscience) or mouse anti-IL-17F (SKU #s including, but not limited to, 7471 and 8471 , eBioscience). The neutralizing or function-blocking antibody against an IL-17 may be a reformulated or humanized derivative of one or more human anti- IL- 17A (SKU #s including, but not limited to, 7178, 7179, 8179, 7176, 7976, and 7876 or human anti-IL-17F SKU #s including, but not limited to, 8479, eBioscience). Preferably, the neutralizing or function-blocking antibody against an IL- 17 may be a reformulated or humanized derivative of, or bind to the epitope of functional grade purified anti-human IL-17A antibody (Clone: eBio64CAP17, Catalog # 16-7178. eBioscience).

Alternatively, the composition may comprise an intrabody that binds to the IL- 17 receptor complex or any synthetic intermediate of IL- 17 or the IL- 17 receptor complex. The composition may alternatively, or in addition, comprise a soluble fragment of the IL- 17 receptor complex which binds IL-17.

Exemplary polypeptides include, but are not limited to, fusion and/or chimeric proteins capable of disrupting IL- 17 function. Moreover, the composition comprises morpholino antisense oligonucleotides, microRNAs (miRNAs), short hairpin RNA (shRNA), or short interfering RNA (siRNA) to silence gene expression.

Contemplated function-blocking antibodies targeted against an IL- 17 cytokine or an

IL- 17 receptor are monoclonal or polyclonal. The contemplated antibody binds to one or more sequences within an IL- 17 or IL- 17 receptor polypeptide. The antibody is alternatively an intrabody. In some embodiments, the antibody comprises a single chain, a humanized, a recombinant, or a chimeric antibody. One or more compounds are directly or indirectly conjugated onto this antibody.

Antagonists of IL- 17 and/or its receptor complex are administered either simultaneously or sequentially with an antagonist of IL-1 and/or its receptor.

Human IL-17 is encoded by the mRNA sequence of NCBI Accession No. NM 002190, alternatively called IL-17A. Human IL-17 is encoded by the amino acid sequence of NCBI Accession No. NM_002190, alternatively called IL-17A. Human IL-17B is encoded by the mRNA sequence of NCBI Accession No. NM_014443. Human IL- 17B is encoded by the amino acid sequence of NCBI Accession No. NM_014443. Human IL-17C is encoded by the mRNA sequence of NCBI Accession No. NM_013278. Human IL- 17C is encoded by the amino acid sequence of NCBI Accession No. NM_013278. Human IL- 17D is encoded by the mRNA sequence of NCBI Accession No. NM_138284. Human IL-17D is encoded by the amino acid sequence of NCBI Accession No. NM_138284. Human IL- 17E is encoded by the mRNA sequence of NCBI Accession No. AF305200. Human IL- 17E is encoded by the amino acid sequence of NCBI Accession No. AF305200. Human IL- 17F is encoded by the mRNA sequence of NCBI Accession No. NM 052872. Human IL-17F is encoded by the amino acid sequence of NCBI Accession No. NM_052872.

IL-17 receptor antagonist (IL-17RA) is encoded by the mRNA sequence of NCBI Accession No. NM 014339. IL- 17RA is encoded by the amino acid sequence of NCBI Accession No. NMJ4339. IL- 17RB is encoded by the mRNA sequence of NCBI Accession No.
NM_018725. IL-17RB is encoded by the amino acid sequence of NCBI Accession No. NM_018725. IL-17RC, transcript variant 1 , is encoded by the mRNA sequence of NCBI Accession No. NM l 53461. IL- 17RC, transcript variant 1, is encoded by the amino acid sequence of NCBI Accession No. NM_153461. IL-17RC, transcript variant 2, is encoded by the mRNA sequence of NCBI Accession No. NMJ 53460. IL- 17RC, transcript variant 2, is encoded by the amino acid sequence of NCBI Accession No. NM_153460. IL- 17RC, transcript variant 3, is encoded by the mRNA sequence of NCBI Accession No. NM_032732. IL-17RC, transcript variant 3, is encoded by the amino acid sequence of NCBI Accession No. NM_032732. IL- 17RD, transcript 1, is encoded by the mRNA sequence of NCBI Accession No. NMJ)01080973. IL-17RD, transcript 1, is encoded by the amino acid sequence of NCBI

Accession No. NMJ)Ol080973. IL-17RD, transcript 2, is encoded by the mRNA sequence of NCBI Accession No. NM Ol 7563. IL-17RD, transcript 2, is encoded by the amino acid sequence of NCBI Accession No. NM_017563. IL- 17RE, transcript variant 1 , is encoded by the mRNA sequence of NCBI Accession No. NM l 53480. IL- 17RE, transcript variant 1, is encoded by the amino acid sequence of NCBI Accession No. NM_153480. IL- 17RE, transcript variant 2, is encoded by the mRNA sequence of NCBI Accession No. NM_153481. IL- 17RE, transcript variant 2, is encoded by the amino acid sequence of NCBI Accession No. NM_153481. IL- 17RE, transcript variant 5, is encoded by the mRNA sequence of NCBI Accession No. NM_153483. IL- 17RE, transcript variant 5, is encoded by the amino acid sequence of NCBI Accession No. NM_153483.

To study the effect of IL-17 blockade on corneal neuropathy, an art-recognized murine model of dry eye disease (DED) was used. As described above, DED was induced in female C57BL/6 mice by exposure to a desiccating environment in a controlled environment chamber and to systemic scopolamine (Figure 8A). After induction of DED for 9-10 days, whole mount corneas were immunostained for nerve-specific β-tubulin-III, and then epifluorescence micrographs were captured and processed under an automated Matlab based software nerve quantification. Nerve fiber length and nerve fiber tortuosity (indices of neuroregeneration/neurodegeneration) were analyzed as described below.

Both the anti-cytokine therapies, including IL-1Ra and anti-IL17 prevented loss of nerve fibers in DED corneas (Figure 8B). By contrast, use of a lubricating drop ("Vehicle") or CsA showed ~2-fold decrease in the fiber length compared to those in normal corneas, suggesting that standard treatments against DED (lubrication or topical cyclosporine) do not protect significantly against nerve damage. Similarly, IL-1Ra and anti-IL17 therapies maintain the nerve fiber tortuosity levels similar to that seen in normal corneas, whereas DED corneas treated with vehicle or CsA show ~2-fold increase in the nerve fiber tortuosity as compared to the normals (Figure 8C).

These results demonstrate that blockade of Interleukin-1 (IL-1) either directly using topical IL-1 receptor antagonist (IL-1Ra) or indirectly by blocking IL-17 (a potent inducer of IL-1β by target cells) using anti-IL17-antibody inhibits corneal neuropathy, including the symptoms of nerve loss (fiber length) and nerve tortuosity. The treatments that block IL-1 and IL-17 promote nerve fiber length, but suppress nerve fiber tortuosity.

The nerve tortuosity data and the nerve fiber length data described above indicate that conventional therapies for DED (topical lubricating tear ointment or topical cyclosporine-A) do not protect significantly against nerve damage. Although ocular surface inflammation

associated with DED is often correlated with elevated levels of tear nerve growth factor, which is typically reduced with steroids such as 0.1% prednisolone, the results above indicate that such therapy are ineffective at inducing corneal nerve regeneration. Thus, administration of such immunosuppressive agents (*e.g.*, macrolides such as cyclosporin A (*e.g.*, Restasis®), or corticosteroids such as prednisolone) are preferably not administered with the compositions described herein.

Example 7: Combination therapy blockade of IL-1 and IL-17 enhances corneal nerve regeneration IL-1 is a major initiator of the inflammatory process upstream of T cell activation and plays a crucial role in precipitating the inflammation by promoting the induction or expansion of IL-17-secreting T cells. IL-1 and IL-17 work synergistically and enhance secretion of each other *in vivo*.

An IL-17 blocking treatment is applied to a cornea, along with an IL-1 blocking treatment. The co-administration of IL-1 and IL-17 blocking treatment enhances corneal nerve regeneration such that the amount of nerve fibers associated with damaged corneas is increased compared to untreated corneas. The co-administration of IL-1 and IL-17 blocking treatment synergistically enhances corneal nerve regeneration in the case of immune-mediated corneal nerve damage.

Example 8: Efficacy of topical application of IL-1Ra in ocular surface inflammatory disorders in a human

An IL-1Ra open label study was utilized to determine the efficacy of IL-1Ra in treating ocular surface inflammatory disorders in a human. Seventy patients were enrolled in the study and various numbers of patients were available for monthly checkups as follows: month 1 (44 patients), month 3 (37 patients), month 5 (22 patients), and month 7 (17 patients). None of these patients had severe meibomian gland dysfunction (MGD, also called posterior blepharitis) defined as grade 3 meibomian secretions (secretions retain shape after expression), or grade 4 lid margin disease (marked diffuse redness of both lid margins and skin), or grade 4 conjunctival hyperemia (marked dark redness of the palpebral and/or bulbar conjunctiva). Of note, patients with MGD/meibomian gland dysfunction alone do not develop significant corneal neuropathy (Foulks and Bron, 2003 Ocul Surf, 107-26).

As shown in Figures 9A and 9B, corneal staining was utilized to measure ocular surface disease treated with topical IL-1 receptor antagonist. Specifically, the application of fluorescein was used to detect epithelial damage in the cornea, and each patient's disease severity was graded using the Oxford scale. The data demonstrate a significant reduction in staining (severity of disease) with topical blockade of IL-1 using the IL-1 receptor antagonist.

Specifically, a significant change was observed from baseline to 7 months follow-up after treatment with IL-1 receptor antagonist.

As depicted in Figures 10A and 10B, lisamine green staining was utilized to detect damage to the conjunctival epithelium, and each patient's disease was graded using the standardized Oxford scale. A significant reduction in interpalpebral (conjunctival) staining (severity of disease) was observed from baseline to 7 months follow-up after treatment with IL-1 receptor antagonist. Ocular surface disease index (OSDI) is a validated instrument for measuring dry eye disease symptoms' severity and effect on vision-related function. The score ranges from 0 (no symptoms) to 100 (maximal symptoms and visual dysfunction in all categories), with higher scores representing greater disability. OSDI was determined for each patient treated with IL-1 receptor antagonist (Figures 11A and 11B). OSDI score decreased significantly from baseline to 7 months follow-up after treatment with IL-1 receptor antagonist.

The Schirmer test measures the amount of tear produced by a patient's eye. The test is performed by placing a special scaled filter paper strip between the lower eyelid and the eyeball for 5 minutes. As shown in Figure 12, tear volume increased from below 6 mm at baseline to
~9 mm at 7 months of follow-up. The data suggest an overall trend toward higher tear secretion with topical blockade of IL-1 with IL-1 receptor antagonist.

Figure 13 shows confocal micrographs of corneas from patients with dry eye disease before and after treatment with topical vehicle or topical IL-1Ra. One month of IL-Ra treatment promoted corneal nerve regeneration (marked with white arrows). By contrast, one month of vehicle treatment (lubricating drops) did not promote corneal nerve regeneration. These data support the observation made in mice (above) that selective blockade of cytokines with pathogenic roles in dry eye disease (IL-1, IL-17) provide a level of neuroprotection not observed with standard treatments.

OTHER EMBODIMENTS

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

The patent and scientific literature referred to herein establishes the knowledge that is available to those with skill in the art. All United States patents and published or unpublished United States patent applications cited herein are incorporated by reference. All published foreign patents and patent applications cited herein are hereby incorporated by reference. Genbank and NCBI submissions indicated by accession number cited herein are hereby incorporated by reference. All other published references, documents, manuscripts and scientific literature cited herein are hereby incorporated by reference.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

What is claimed is:

CLAIMS

1. A method for protecting or regenerating corneal nerves in a subject in need thereof, comprising the steps of:

(a) identifying a subject with corneal nerve damage or loss; and

(b) locally administering to the cornea of said subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine, thereby enhancing corneal nerve regeneration and reducing the development of abnormalities in nerve morphology or density.

2. A method for minimizing or preventing damage or loss of corneal nerves in a subject in need thereof, comprising the steps of:

(a) identifying said subject at risk of exposure to corneal nerve damage or loss; and

(b) locally administering to the cornea of said subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine prior to said exposure, thereby decreasing nerve degeneration and reducing or preventing the development of abnormalities in nerve morphology or density.

3. The method of claim 1 or 2, wherein said activity comprises binding of an inflammatory IL-1 cytokine to an IL-1 receptor.

4. The method of claim 1, wherein said subject is identified as having corneal nerve damage or loss that results from a congenital defect, disease, trauma, medical or surgical procedure.

5. The method of claim 1, wherein said subject is identified as having corneal nerve damage or loss that results from neurotrophic keratitis, herpes simplex, zoster keratitis, diabetes mellitus, trigeminal nerve damage, ocular or orbital or head surgery, head trauma, aneurysm, intracranial neurologic disease, keratorefractive procedures, photorefractive keratectomy (PRK), laser in situ keratomileusis (LASIK), congenital defect, ocular surface disease, dry eye syndrome, a non-ophthalmic disorder, a non-ophthalmic procedure, or peripheral neuropathy.

6. The method of claim 2, wherein said subject is identified as being at risk of exposure to corneal nerve damage or loss that could result from disease, trauma, or a medical procedure.

7. The method of claim 2, wherein said subject is identified as being at risk of exposure to corneal nerve damage or loss that could result from neurotrophic keratitis, herpes simplex, zoster keratitis, diabetes mellitus, trigeminal nerve damage, orbital or head surgery, head trauma, aneurysm, intracranial neurologic disease, keratorefractive procedures, photorefractive keratectomy (PRK), laser in situ keratomileusis (LASIK), ocular surface disease, dry eye syndrome, a non-ophthalmic disorder, a non-ophthalmic procedure, or peripheral neuropathy.

8. The method of claim 1 or 2, further comprising the step of identifying a subject with a sign or symptom of corneal nerve damage or loss.

9. The method of claim 8, wherein a sign of corneal nerve damage or loss is a decrease of corneal innervation or sensation, a reduction in the number of nerve fibers or bundles innervating the cornea, death of neurons innervating the cornea, a decrease or loss of neurotransmitter release, a decrease or loss of nerve growth factor release, abnormal tearing reflexes, abnormal blink reflexes, abnormal nerve morphology, appearance of abnormal nerve sprouts, abnormal tortuosity, increased bead-like nerve formations, thinning of nerve fiber bundles, or thickening of nerve fiber bundles.

10. The method of claim 8, wherein a symptom of corneal nerve damage or loss is abnormal tear production or dryness, abnormal blinking, and difficulty or loss of ability to focus, decreased or lost visual acuity, or decreased or lost corneal sensitivity.

11. The method of claim 3, wherein said composition that inhibits binding of an inflammatory IL-1 cytokine to an IL-1 receptor comprises an amino acid sequence of SEQ ID NO: 15 or SEQ ID NO: 16.

12. The method of claim 1 or 2, wherein said composition is present in a concentration of 0.1-10 % (mg/ml).

13. The method of claim 1 or 2, wherein said composition is present in a concentration of 2.5 % (mg/ml) or 5 % (mg/ml).

14. The method of claim 1 or 2, wherein the form of said composition is a solid, a paste, an ointment, a gel, a liquid, an aerosol, a mist, a polymer, a film, an emulsion, or a suspension.

15. The method of claim 1 or 2, wherein said composition is administered topically.

16. The method of claim 1 or 2, wherein said method does not comprise systemic administration or substantial dissemination to non-ocular tissue.

17. The method of claim 1 or 2, wherein said composition further comprises a compound selected from the group consisting of a physiological acceptable salt, poloxamer analogs with carbopol, carbopol/HPMC, carbopol-methyl cellulose, a mucolytic agent, carboxymethylcellulose (CMC), hyaluronic acid, cyclodextrin, and petroleum.

18. The method of claim 17, wherein said mucolytic agent is N-acetyl cysteine.

19. The method of claim 1 or 2, wherein said composition further comprises carboxymethylcellulose (CMC).

20. The method of claim 1 or 2, wherein said composition inhibits the transcription, transcript stability, translation, modification, localization, secretion, or function of a polynucleotide or polypeptide encoding an inflammatory interleukin-1 cytokine or an IL-1 receptor.

21. The method of claim 1 or 2, wherein said composition comprises a polynucleotide, a polypeptide, an antibody, or a small molecule.

22. The method of claim 1 or 2, wherein said composition comprises a morpholino antisense oligonucleotide, microRNA (miRNA), short hairpin RNA (shRNA), or short interfering RNA (siRNA).

23. A method for reducing corneal lymphangiogenesis in a subject in need thereof, comprising the steps of:

(a) identifying a subject with corneal lymphangiogenesis; and

(b) locally administering to the cornea of said subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine, thereby inhibiting the ability of lymphatic vessels to expand within or invade corneal tissue and reducing corneal lymphangiogenesis.

24. A method for minimizing or preventing corneal lymphangiogenesis in a subject in need thereof, comprising the steps of:

(a) identifying said subject at risk of developing lymphangiogenesis onset; and

(b) locally administering to the cornea of said subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine prior to said development, thereby inhibiting the ability of lymphatic vessels to form or expand within, or to invade corneal tissue.

25. A method for reducing the induction of immunity in a cornea of a subject in need thereof, comprising the steps of:

(a) identifying a subject with said induction of immunity; and

(b) locally administering to the cornea of said subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine, thereby inhibiting the ability of lymphatic vessels to expand within or to invade corneal tissue and reducing the induction of immunity, wherein said lymphatic vessels permit the transport of immune cells between said corneal tissue and lymphoid tissues and the initiation of an immune response.

26. A method for minimizing or preventing induction of immunity in a cornea of a subject in need thereof, comprising the steps of:

(a) identifying said subject at risk of developing said immunity; and

(b) locally administering to the cornea of said subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine prior to said development, thereby inhibiting the ability of lymphatic vessels to expand within or to invade corneal tissue and minimizing or preventing said induction of immunity, wherein said lymphatic vessels permit the transport of immune cells between said corneal tissue and lymph nodes and the initiation of an immune response.

27. A method for reducing an autoimmune condition affecting a corneal tissue of a subject in need thereof, comprising the steps of:

(a) identifying a subject with said autoimmune condition; and

(b) locally administering to the cornea of said subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine, thereby inhibiting the ability of lymphatic vessels to expand within or to invade corneal tissue and reducing said autoimmune condition, wherein said lymphatic vessels permit the transport of immune cells between said corneal tissue and lymph nodes and the initiation of an immune response.

28. A method for minimizing or preventing the development of an autoimmune condition affecting a corneal tissue of a subject in need thereof, comprising the steps of:

(a) identifying said subject at risk of developing said autoimmune condition; and

(b) locally administering to the cornea of said subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine prior to said development, thereby inhibiting the ability of lymphatic vessels to expand within or to invade corneal tissue and minimizing or preventing the development of said autoimmune condition, wherein said lymphatic vessels permit the transport of immune cells between said corneal tissue and lymph nodes and the initiation of an immune response.

29. The method of claims 23, 25, or 27, wherein said subject has a dry-eye associated ocular surface disease.

30. The method of claims 24, 26, or 28, wherein said subject is at risk of developing a dry-eye associated ocular surface disease.

31. The method of any one of claims 23-28, wherein said activity comprises binding of an inflammatory IL-1 cytokine to an IL-1 receptor.

32. The method of any one of claims 1, 2, or 23-28, further comprising locally administering an antagonist of interleukin-17 or a receptor thereof.

33. A method for protecting or regenerating corneal nerves in a subject in need thereof, comprising the steps of:

(a) identifying a subject with corneal nerve damage or loss; and

(b) locally administering to the cornea of said subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine and a composition that inhibits an activity

of an inflammatory interleukin-17 cytokine, thereby enhancing corneal nerve regeneration and reducing the development of abnormalities in nerve morphology or density.

FIG. 1A Normal Cornea (Balb/c)



FIG. 1B Vehicle-Treated Cornea (Balb/c); 7 days

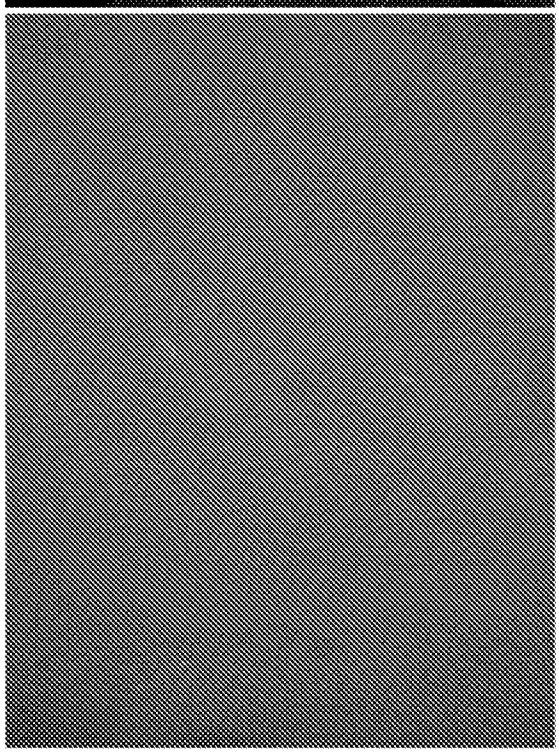
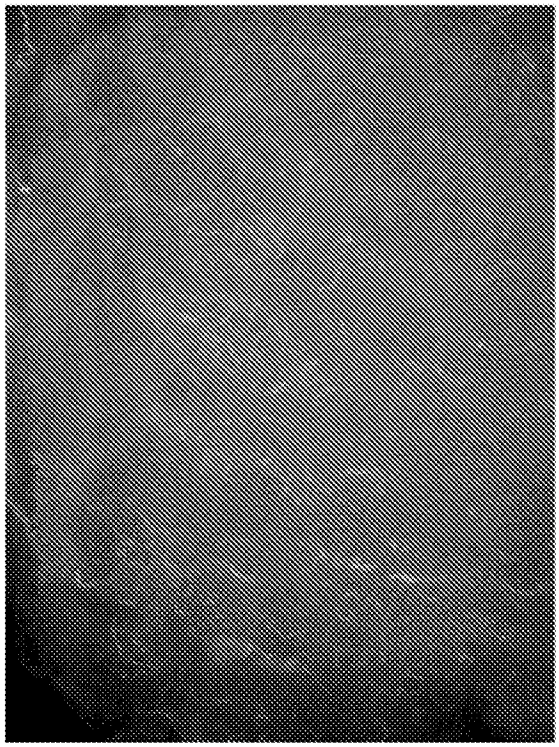


FIG. 1C IL-1Ra-Treated Cornea (Balb/c); 7 days



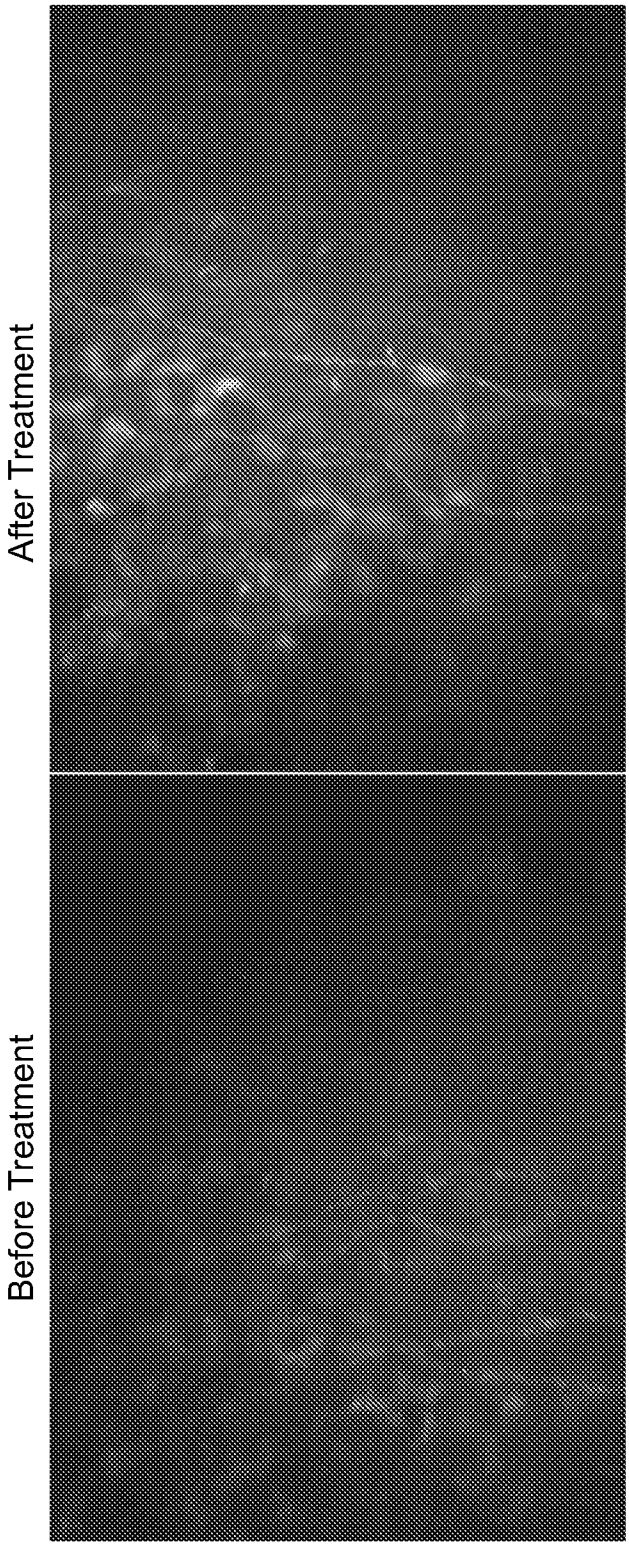


FIG. 2

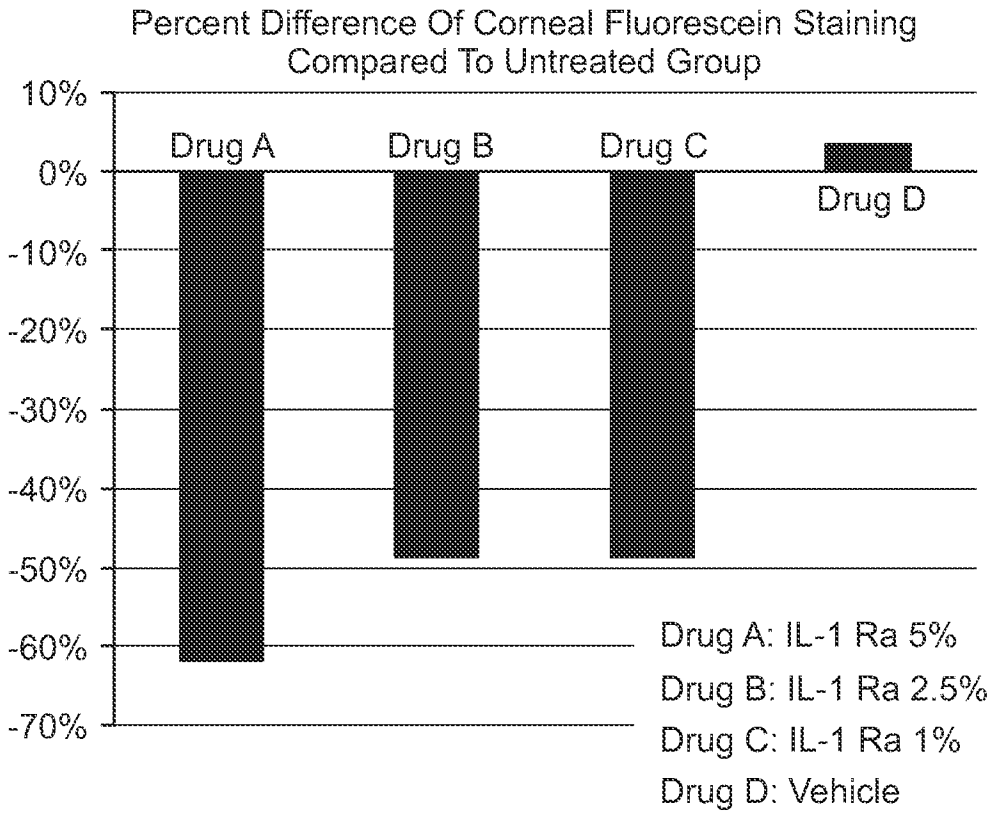

Percent Difference Of Corneal Fluorescein Staining
Compared To Untreated Group
10%
0%
-10%
-20%
-30%
-40%
-50%
-60%
-70%
Drug A
Drug B
Drug C
Drug D
Drug A: IL-1 Ra 5%
Drug B: IL-1 Ra 2.5%
Drug C: IL-1 Ra 1%
Drug D: Vehicle

FIG. 3

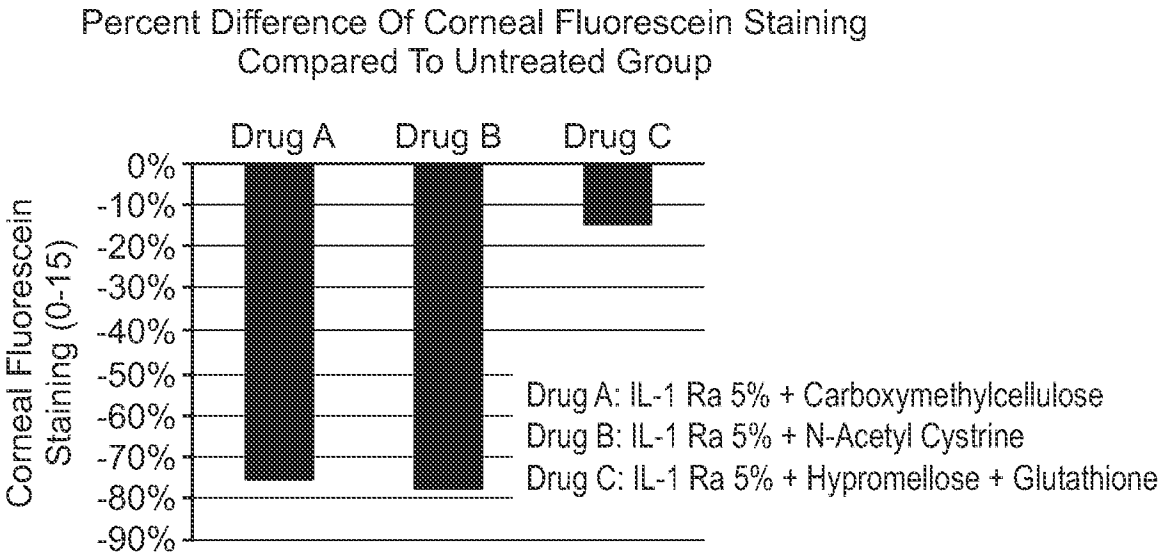
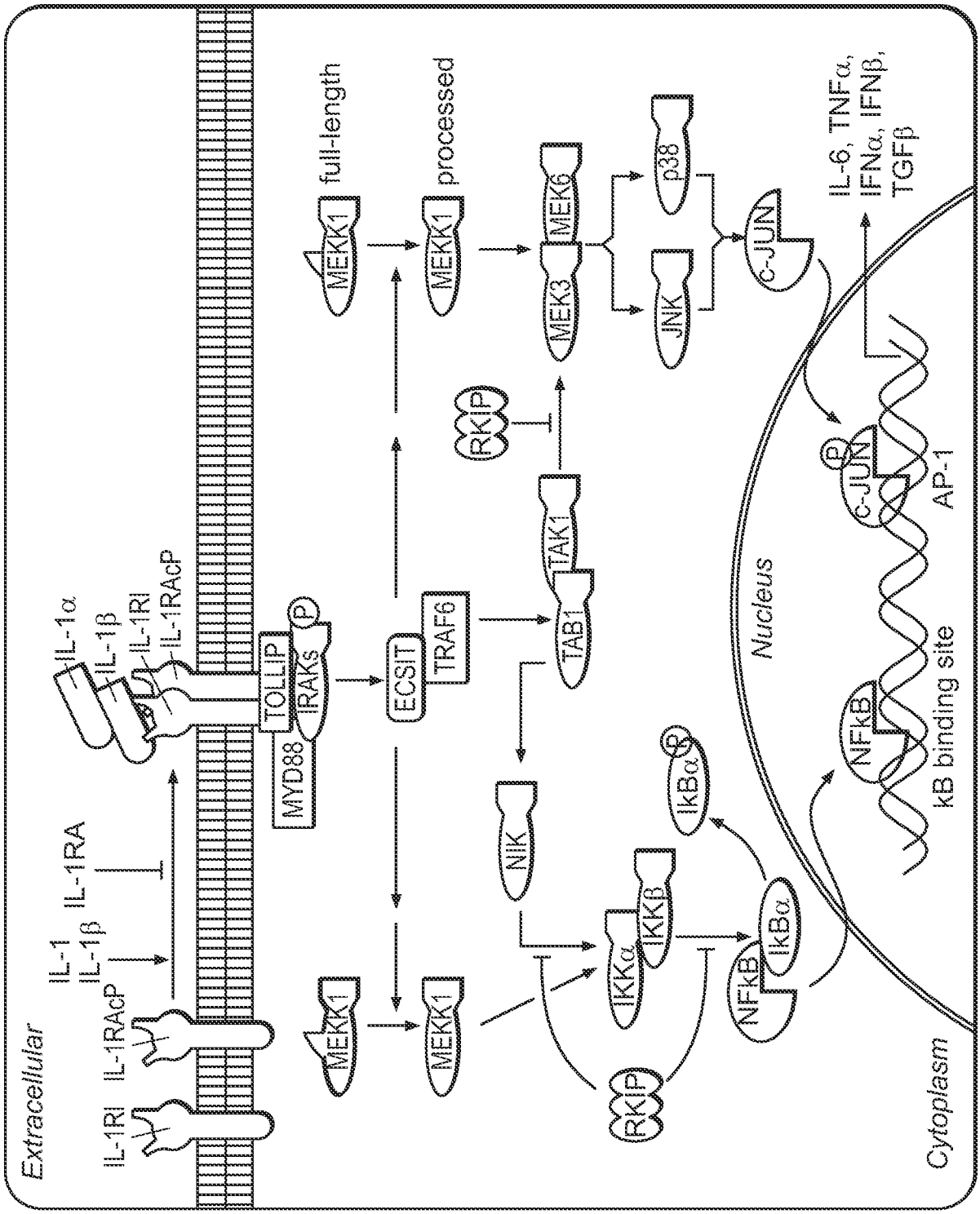

Percent Difference Of Corneal Fluorescein Staining
Compared To Untreated Group
Corneal Fluorescein Staining (0-15)
Drug A
Drug B
Drug C
0%
-10%
-20%
-30%
-40%
-50%
-60%
-70%
-80%
-90%
Drug A: IL-1 Ra 5% + Carboxymethylcellulose
Drug B: IL-1 Ra 5% + N-Acetyl Cystrine
Drug C: IL-1 Ra 5% + Hypromellose + Glutathione

FIG. 4

FIG. 5


Extracellular
IL-1
IL-1β
IL-1RAcP
IL-1RI
IL-1RA
IL-1α
IL-1β
IL-1RI
IL-1RAcP
TOLLIP
MYD88
IRAKs
P
ECSIT
TRAF6
MEKK1
full-length
MEKK1
processed
MEKK1
RKIP
TAK1
TAB1
MEK3
MEK6
p38
JNK
c-JUN
IL-6, TNFα,
IFNα, IFNβ,
TGFβ
NIK
IKKα
IKKβ
IkBα
P
RKIP
NFkB
IkBα
Nucleus
P
c-JUN
AP-1
NFkB
kB binding site
Cytoplasm

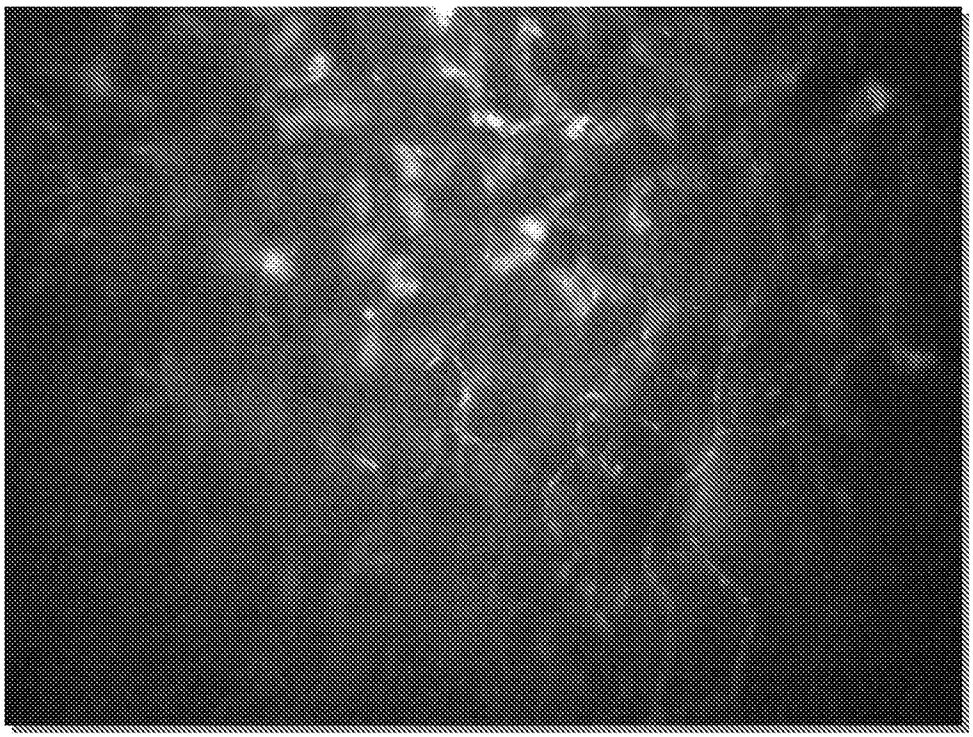


FIG. 6

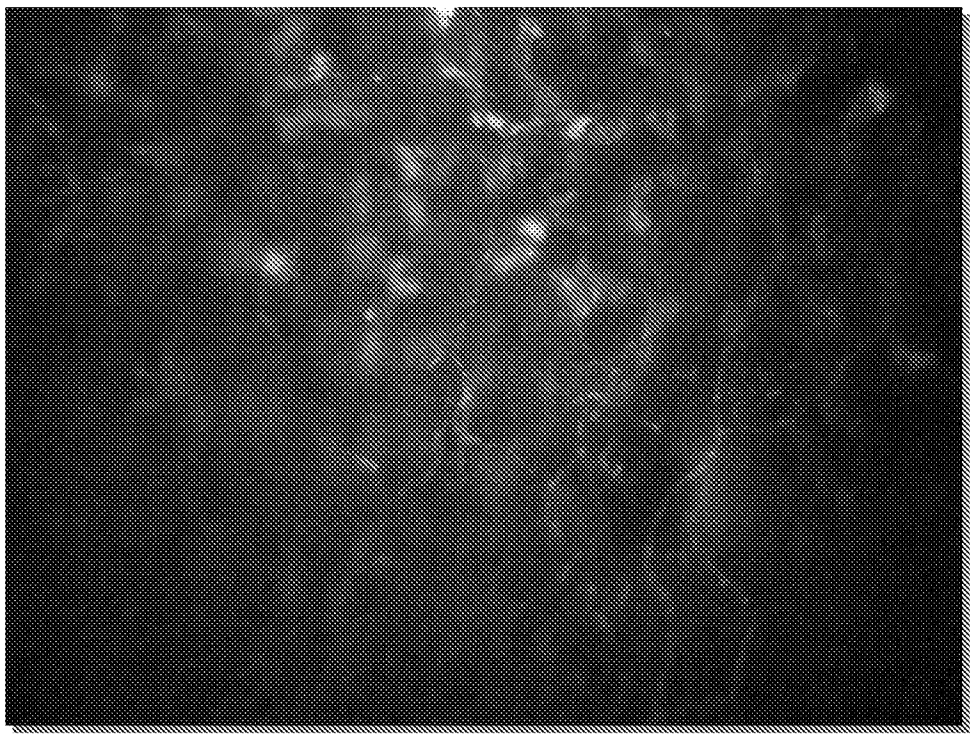


FIG. 7

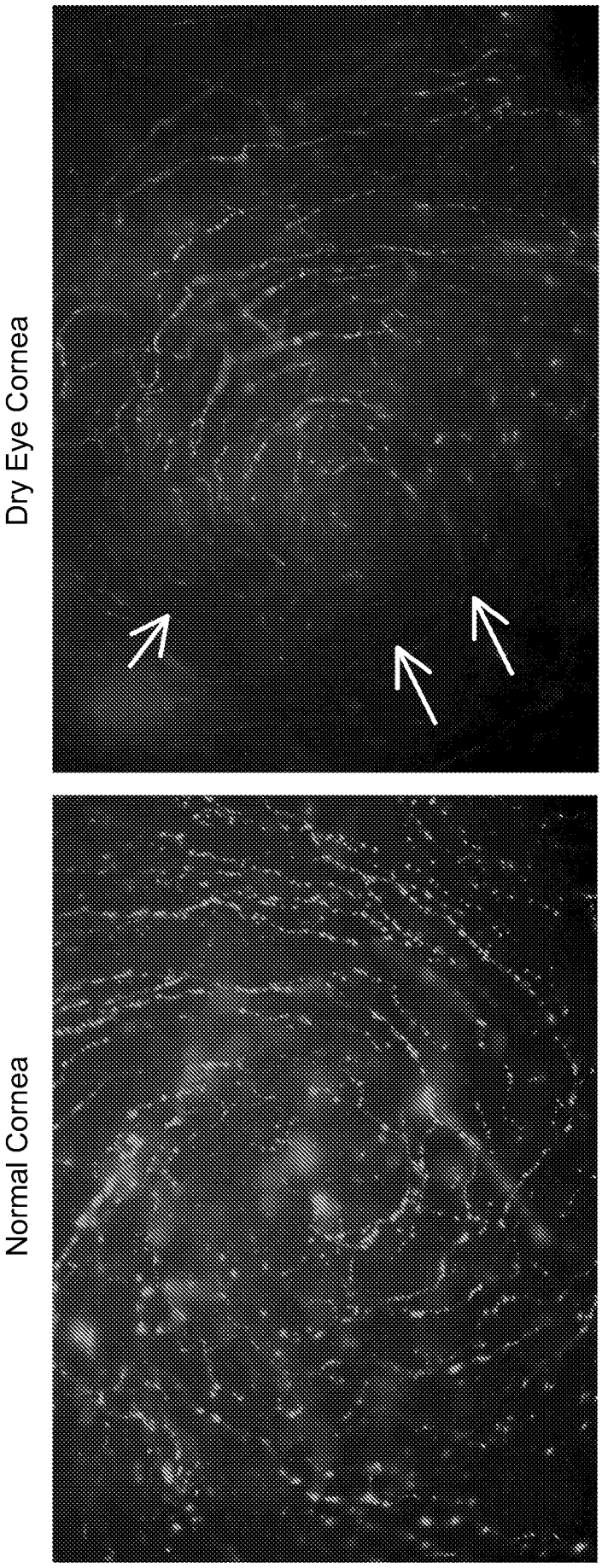


FIG. 8A

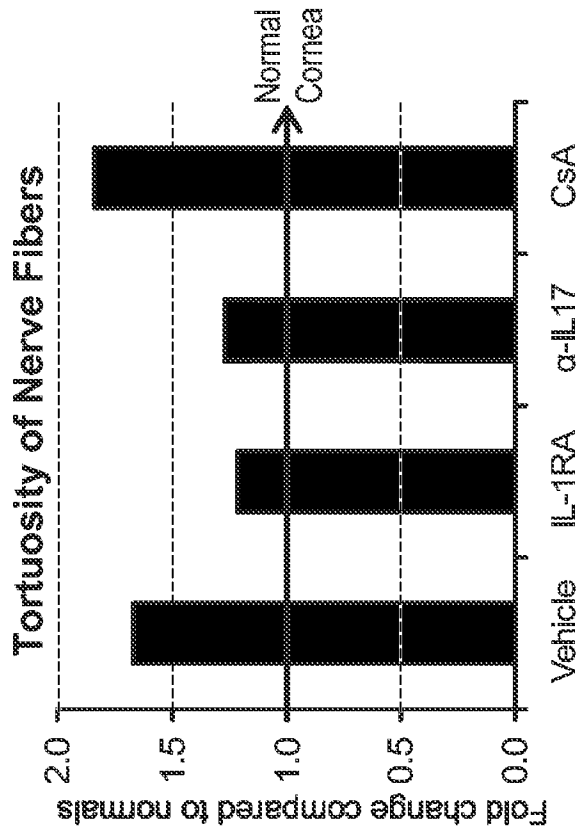

Tortuosity of Nerve Fibers
Normal Cornea
Vehicle
IL-1RA
α-IL17
CsA
0.0
0.5
1.0
1.5
2.0
Fold change compared to normals

FIG. 8C

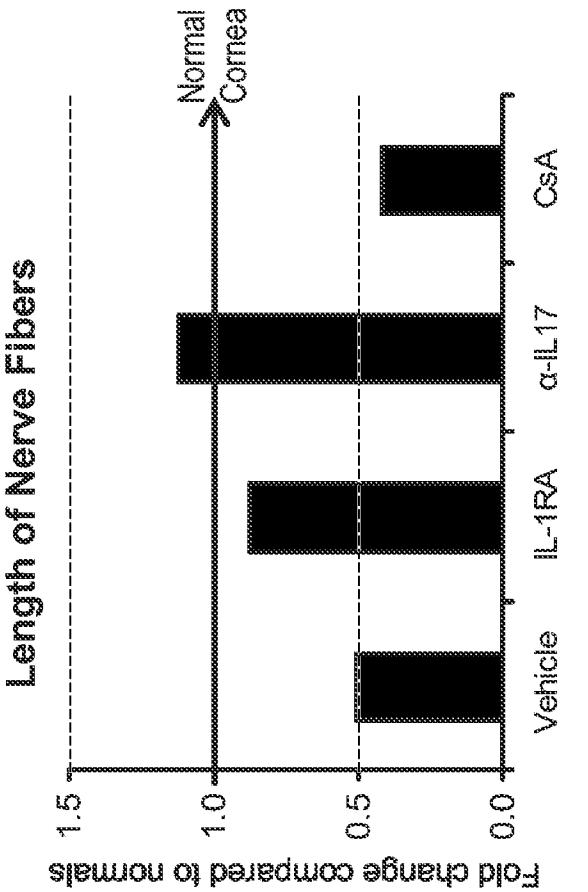

Length of Nerve Fibers
Normal Cornea
Vehicle
IL-1RA
α-IL17
CsA
0.0
0.5
1.0
1.5
Fold change compared to normals

FIG. 8B

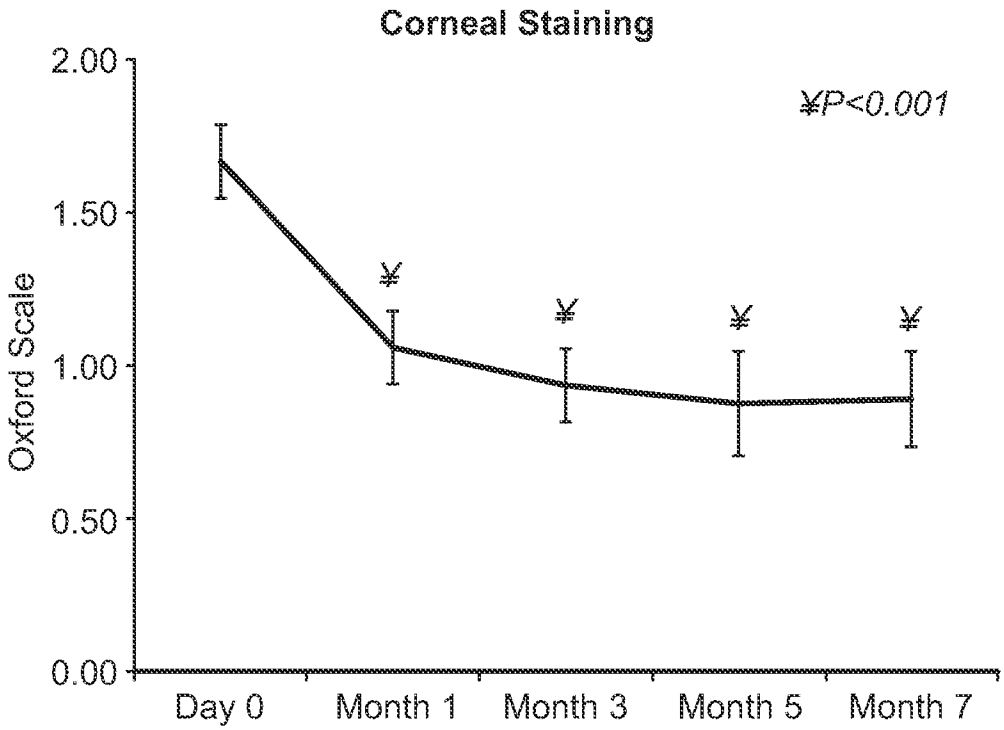

Corneal Staining
¥P<0.001
2.00
1.50
1.00
0.50
0.00
Oxford Scale
¥
¥
¥
¥
Day 0
Month 1
Month 3
Month 5
Month 7

FIG. 9A

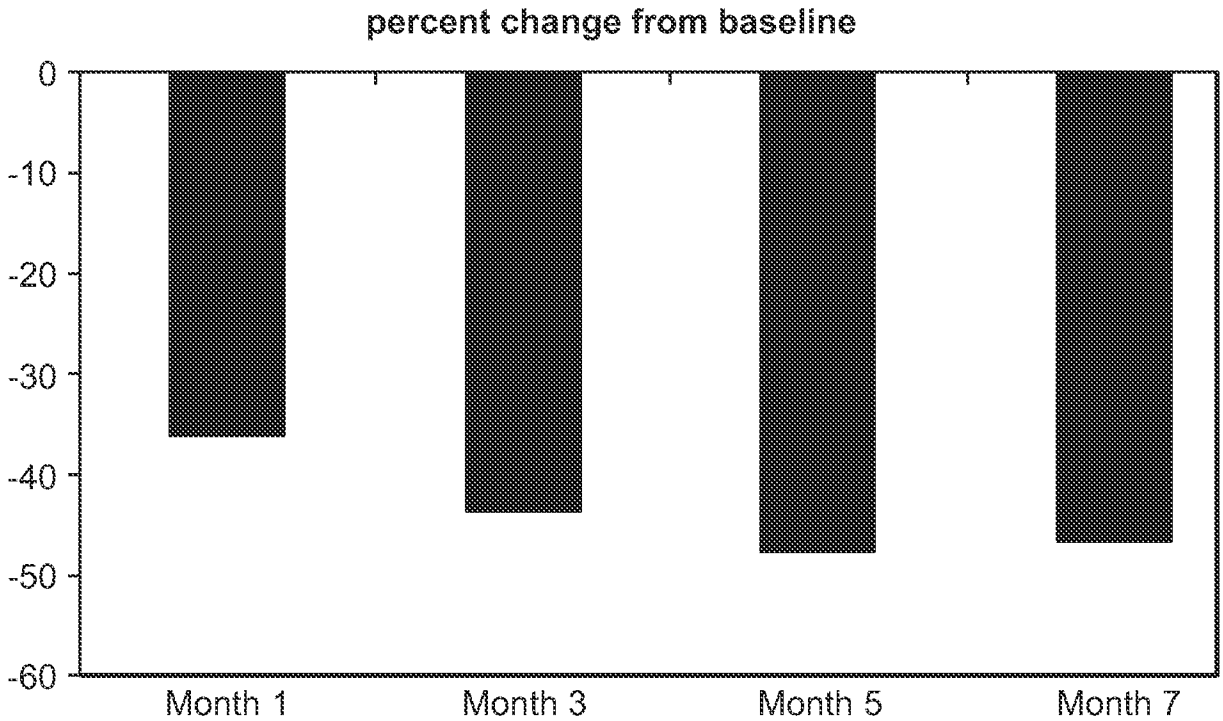

percent change from baseline
0
-10
-20
-30
-40
-50
-60
Month 1
Month 3
Month 5
Month 7

FIG. 9B

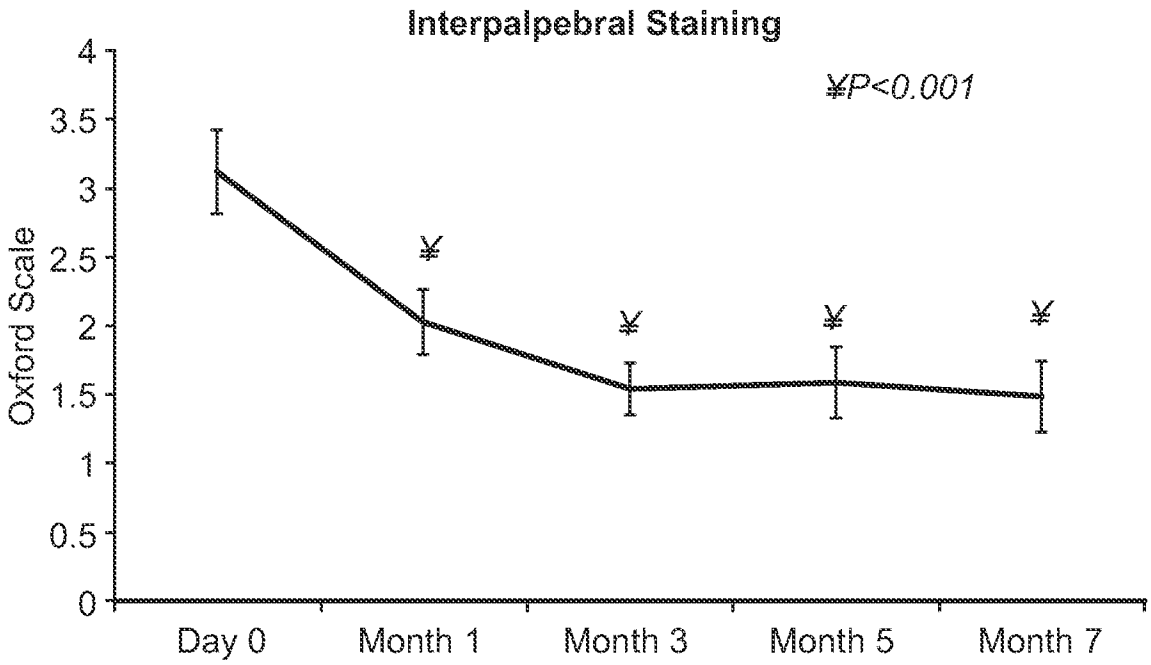


FIG. 10A

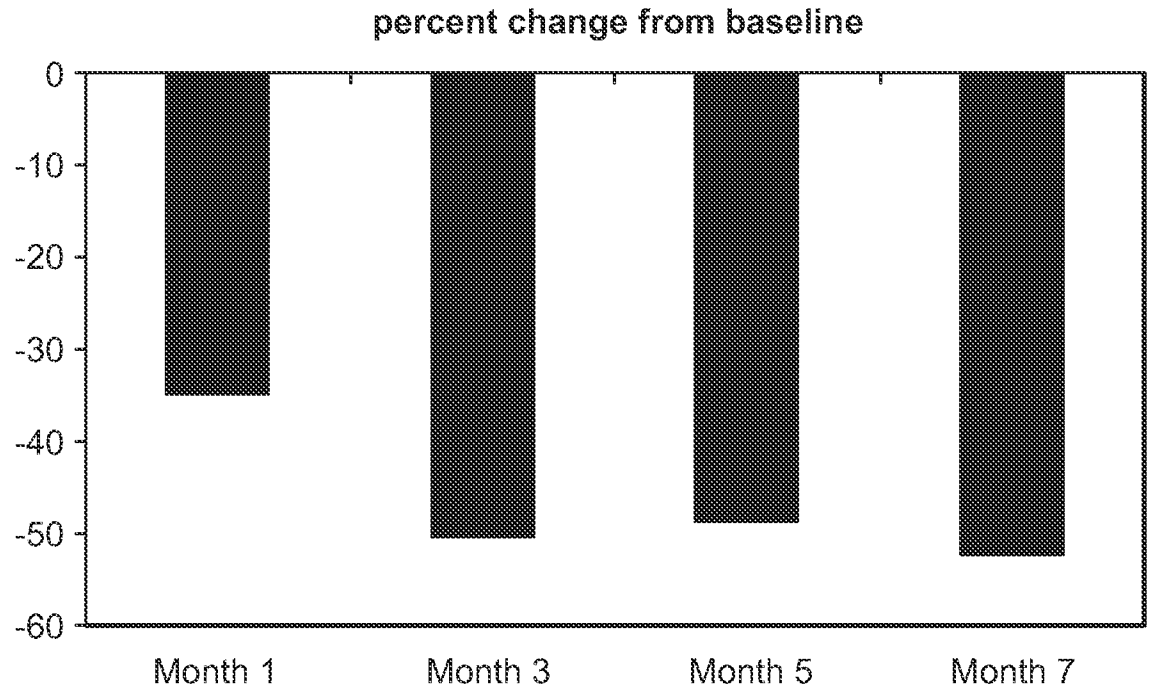


FIG. 10B

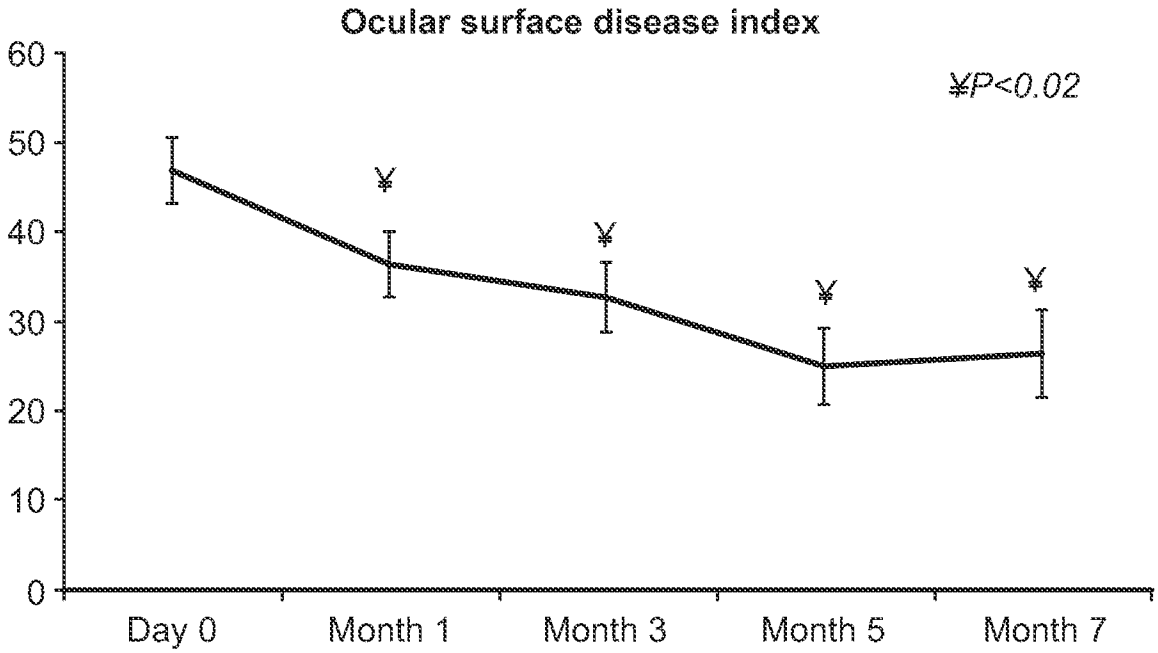


FIG. 11A

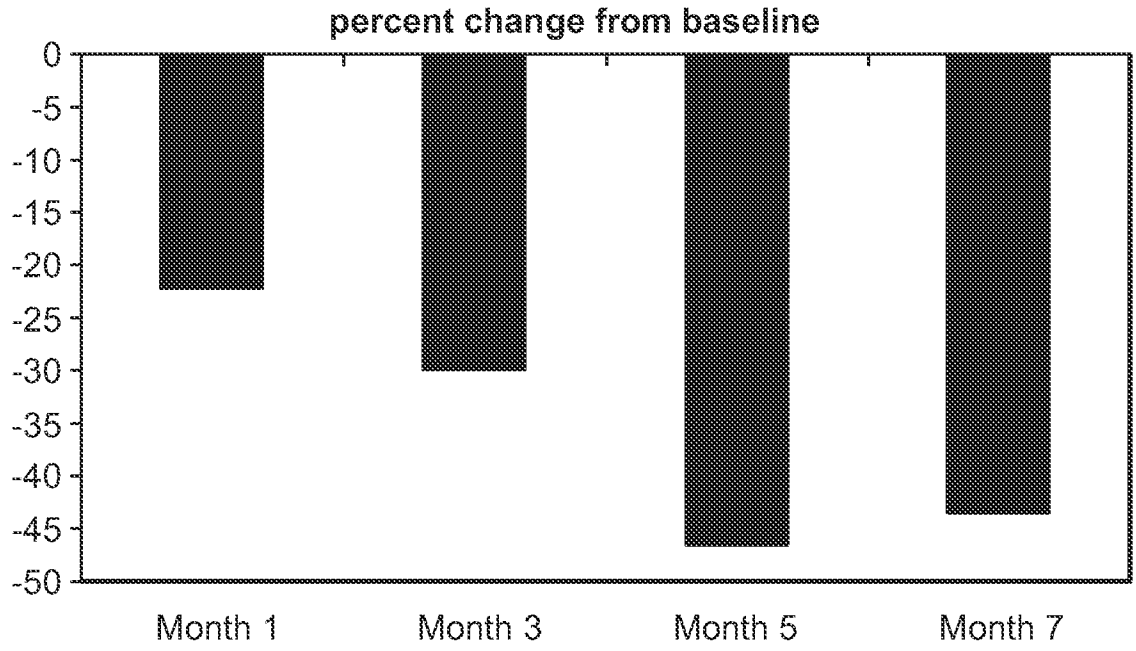


FIG. 11B

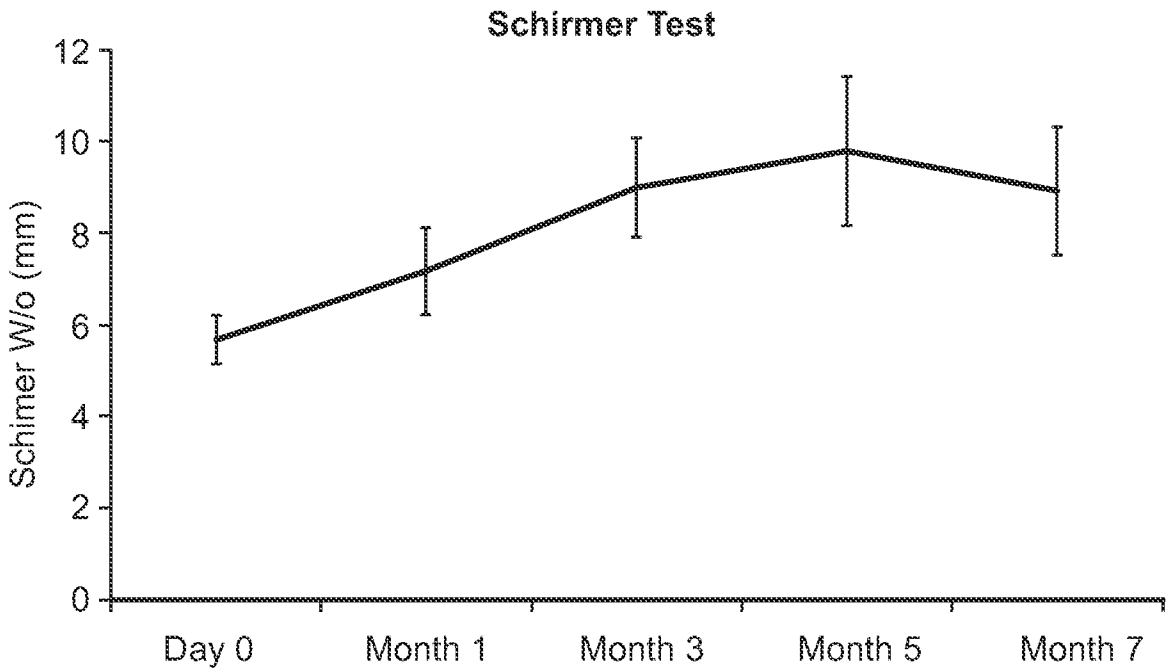

Schirmer Test
Schirmer W/o (mm)
0
2
4
6
8
10
12
Day 0
Month 1
Month 3
Month 5
Month 7

FIG. 12

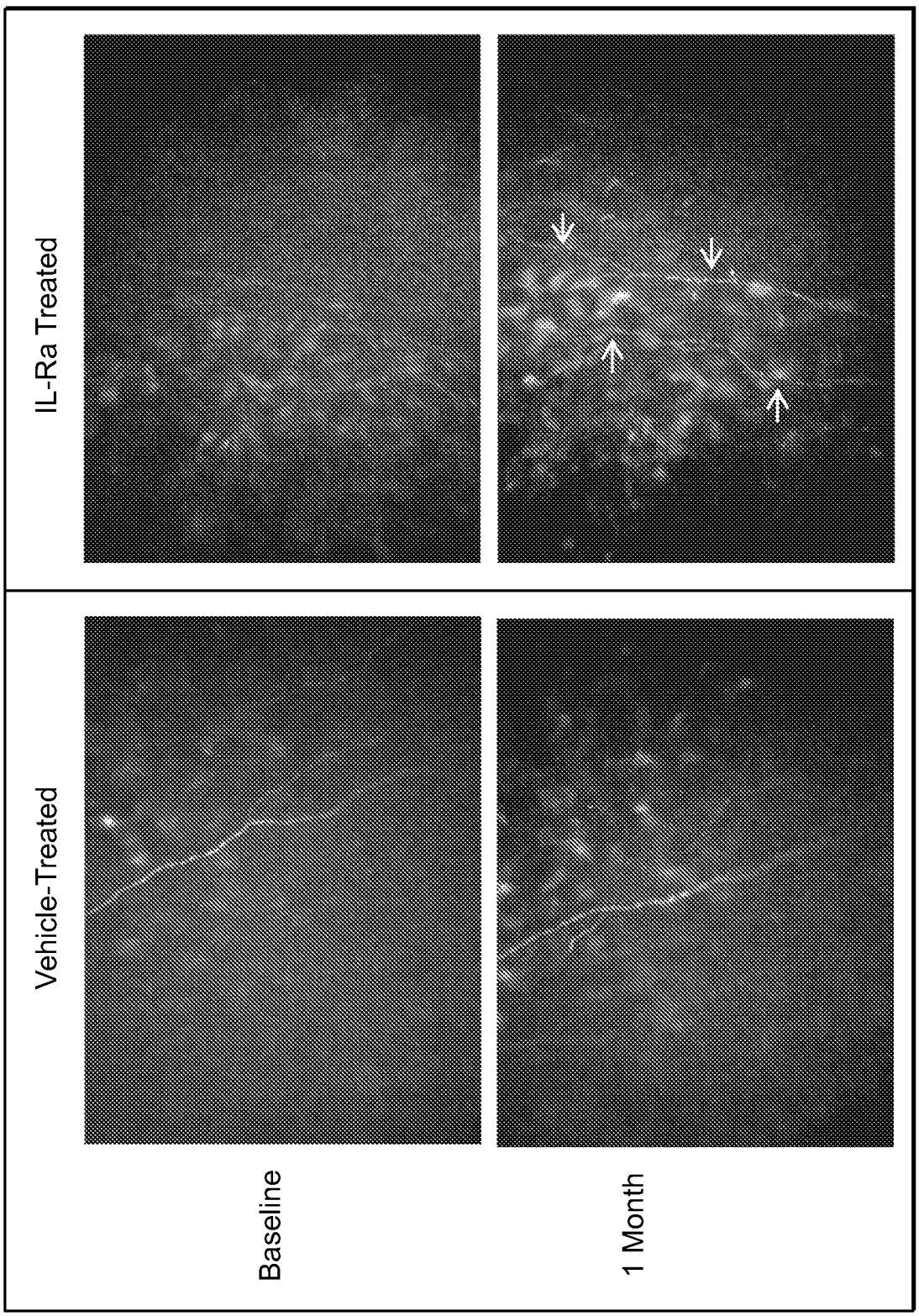


FIG. 13