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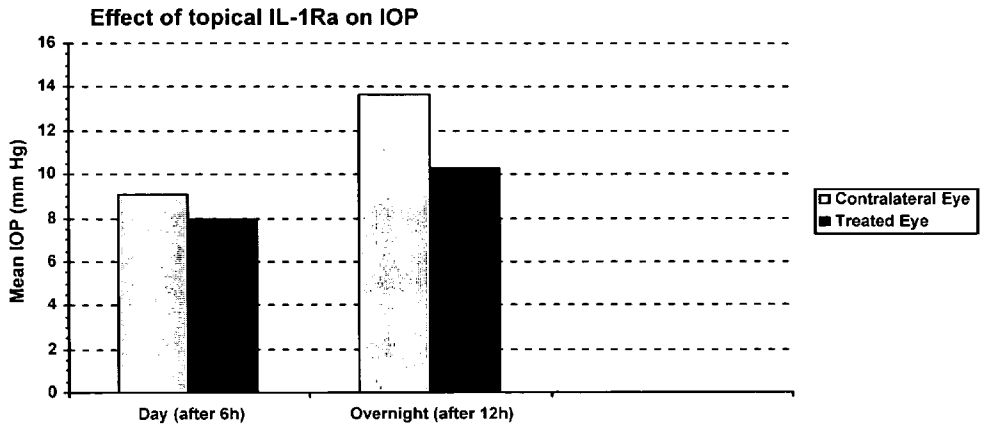
(54) Title: THERAPEUTIC COMPOSITIONS FOR TREATMENT OF INFLAMMATION OF OCULAR AND ADNEXAL TISSUES

FIGURE 3



(57) Abstract: The present invention comprises a composition with means to inhibit the function of the inflammatory cytokine IL-I and methods for using this composition to treat inflammatory disease of ocular and adnexal tissues by topical administration. The present invention also discloses devices for delivering this composition to target tissues.

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THERAPEUTIC COMPOSITIONS FOR TREATMENT OF INFLAMMATION OF OCULAR AND ADNEXAL TISSUES

RELATED APPLICATIONS

[01] This application is related to provisional applications USSN 60/965,135, filed August 16, 2007 and USSN 61/130,687, filed June 2, 2008, the contents of which are each herein incorporated by reference in their entirety.

FIELD OF THE INVENTION

[02] This invention relates generally to the field of ophthalmology.

BACKGROUND OF THE INVENTION

[03] Inflammation of the ocular and adnexal tissues can occur by a variety of mechanisms and is associated, either primarily or secondarily, with a large number of disease conditions. Current treatments for inflammation of these tissues involve the systemic administration of antibiotics, steroids, and immune-system inhibitors. The difficulty of using these systemic drugs becomes apparent through damaging long-term side effects in the case of steroids, long-term drug resistance in the case of antibiotics, or insufficient long-term persistence at the target site in the case of signaling inhibitors. Moreover, the systemic inhibition of signaling within the immune system can have deleterious outcomes for individuals already afflicted with disease, whose susceptibility to additional complications is increased as a result of the systemic use of these treatments.

SUMMARY OF THE INVENTION

[04] The present invention overcomes these obstacles by administering a topical composition comprising one or more antagonists of IL-1 function, or a combination of IL-1 and other inflammatory antagonists, to locally decrease or prevent inflammation of the ocular and adnexal tissues.

[05] A method for inhibiting or reducing the severity of an ocular inflammatory disorder is carried out by locally administering to an ocular or adnexal tissue of a subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine such as binding of an inflammatory IL-1 cytokine to an IL-1 receptor. The subject is identified as suffering from a ocular inflammatory disorder by detecting a sign or symptom selected from the group consisting

of epithelial overexpression of an inflammatory cytokine, vascular hyperplasia or thickening of lid margin, neovascularization of lid margin or corneal periphery, increase of leukocytes at an ocular or adnexal tissue, or overexpression of a matrix metalloprotease at an ocular or adnexal tissue. The method of therapy inhibits or reduces the severity of at least one of these signs or symptoms. For example, the inflammatory disorder is blepharitis. The method comprises administration of a compound that inhibits binding of an inflammatory IL-1 cytokine to an IL-1 receptor. Optionally, the composition also contains an antibiotic compound. The composition does not comprise tetracycline alone, e.g. in the absence of a functional antagonist that specifically targets IL-1. For example, the composition comprises an antibiotic composition administered in combination with a functional antagonist specifically targeting IL-1.

[06] The composition that inhibits binding of an inflammatory IL-1 cytokine to an IL-1 receptor comprises the amino acid sequence of SEQ ID NO: 16. For example, the composition is present in a concentration range of 0.1-10%, with preferred ranges between 1-5%, or 2-2.5% (mg/ml). Exemplary liquid formulations for eye drops contain 2-2.5% (mg/ml) of the composition. Preferred formulations are in the form of a solid, a paste, an ointment, a gel, a liquid, an aerosol, a mist, a polymer, a film, an emulsion, or a suspension. The formulations are administered topically, e.g., the composition is delivered to an ocular or adnexal tissue to directly contact that tissue. The method does not involve systemic administration or substantial dissemination of the composition to non-ocular or non-adnexal tissue. For example, subcutaneous injection of Kineret (see SEQ ID NO: 15 and 16) at 1-2 mg/kg results in an estimated peak blood serum concentration of about 1200-1500 ng/ml 7 hours post-injection. Topical administration of Kineret, as disclosed herein, temporally and spatially restricts absorption of the drug to a much greater degree than subcutaneous injection. The systemic dissemination of a topically administered Kineret composition contributes significantly less drug to the blood serum concentration than a subcutaneous injection.

[07] 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, carboxymethylcellulose (CMC), hyaluronic acid, cyclodextrin, and petroleum.

[08] The invention comprises a composition that inhibits an activity of an inflammatory interleukin-1 cytokine, the composition being in the form of 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 present at a concentration of 0.1 - 10% (mg/ml). An exemplary composition includes a polypeptide comprising the amino acid sequence of SEQ ID NO: 16.

[09] A method for inhibiting or reducing the severity of an ocular inflammatory disorder is also carried out by locally administering to an ocular or adnexal tissue of a subject a composition comprising a polynucleotide, a polypeptide, an antibody, a compound, or a small molecule that inhibits the transcription, transcript stability, translation, modification, localization, secretion, or function of a polynucleotide or polypeptide encoding an inflammatory interleukin-1 cytokine (IL-1a, SEQ ID NO: 1 and 2, or IL-1b, SEQ ID NO: 3 and 4), an IL-1 receptor (type 1, SEQ ID NO: 17 and 18, or type 2, SEQ ID NO: 17-21), an IL-1R binding protein (IL-1RAP, SEQ ID NO: 24-27), or an IL-1R downstream signaling effector (IRAK1, SEQ ID NO: 28-33).

[10] Alternatively, the composition inhibits or enhances 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.

[11] 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 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.

[12] In another embodiment, 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 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) and subsequent induction of an inflammatory response. Thus, the inhibition of IRAK1 expression and/or function provides an additional mechanism for inhibiting an IL-1-mediated immune response.

[13] The composition comprises 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, or IRAK1. Moreover the composition comprises 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).

[14] The composition comprises microRNA molecules adapted for topical administration to ocular or adnexal tissues 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).

[15] Exemplary polypeptides to be adapted for topical administration to ocular or adnexal tissues 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).

[16] Exemplary antibodies to be adapted for topical administration to ocular or adnexal tissues 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).

[17] 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 ocular or adnexal tissues is ZnPP (IL-1 blocker zinc protoporphyrin, naturally-occurring metabolite, Yamasaki et al. Stroke. 1995; 26:676-681).

[18] The composition does or, alternatively, does not comprise one or more antibiotic compositions to be used in combination with an antagonist of IL-1 function. The antibiotic and IL-1 antagonist compositions are administered simultaneously or sequentially. Exemplary antibiotic compositions used for combination-therapy with antagonists of IL1-mediated inflammation include but are not limited to, amikacin, gentamicin, kanamycin, neomycin, netilmicin, streptomycin, tobramycin, teicoplanin, vancomycin, azithromycin, clarithromycin,

clarithromycin, dirithromycin, erythromycin, roxithromycin, troleandomycin, amoxicillin, ampicillin, azlocillin, carbenicillin, clozacillin, dicloxacillin, flucozacillin, mezlocillin, nafcillin, penicillin, piperacillin, ticarcillin, bacitracin, colistin, polymyxin B, ciprofloxacin, enoxacin, gatifloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, oflazacin, trovafloxacin, mafenide, sulfacetamide, sulfamethizole, sulfasalazine, sulfisoxazole, trimethoprim, cotrimoxazole, demeclocycline, soxycycline, minocycline, oxytetracycline, or tetracycline.

[19] The composition comprises an antagonist of an IL-1 cytokine or an IL-1 receptor, administered simultaneously or sequentially with a second immunosuppressive composition. The immunosuppressive compound comprises cyclosporin A or analogs thereof a concentration of 0.05 - 4.0 % (mg/ml). Alternatively, or in addition, the immunosuppressive composition comprises a glucocorticoid, a cytostatic agent, an alkylating agent (nitrogen mustards/cyclophosphamide, nitrosoureas, platinum compounds), an antimetabolic agent (methotrexate, any folic acid analog, azathioprine, mercaptopurine, any purine analog, any pyrimidine analog, any inhibitor of protein synthesis), a cytotoxic antibiotic (dactinomycin, an anthracycline, mitomycin C, bleomycin, mithramycin), a polyclonal antibody (Atgam®, Thympglobuline®, any antibody against the antilymphocyte or antithymocyte antigens), a monoclonal antibody (OKT3®, any antibody against the T-cell receptor, any antibody against IL-2, basiliximab/Simulect®, declizumab/Zenapax®), Tacrolimus/Prograf™/FK506, Sirolimus/Rapamune™/Rapamycin, interferon beta, interferon gamma, an opioid, a TNFα binding protein, mycophenolate, or FTY720.

[20] The composition comprises 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, 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).

[21] 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).

[22] 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 intended ocular or adnexal target tissue 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.

[23] 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).

[24] 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.

[25] Compositions comprise 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 ocular or adnexal tissue 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.

[26] The composition comprises an antagonist of IL-1 and/or IL-1R function in combination with other inhibitory elements. Antagonists of IL-1 and/or IL-1R and other inhibitory elements are administered simultaneously or sequentially. In one embodiment, the composition comprises an antagonist of IL-1 and/or IL-1R function and an antagonist of tumor necrosis factor alpha (TNFα). Exemplary functional blockers of TNFα include, but are not limited to, recombinant and/or soluble TNFα receptors, monoclonal antibodies, and small molecule antagonists and/or inverse agonists. One or more commercially-available TNF-α blocking agents are reformulated for topical administration in this embodiment. Exemplary commercial TNF-α blocking agents used for reformulation include, but are not limited to, etanerept/Embrel, infliximab/Remicade, and adalimumab/Humira. Alternatively, the composition comprises an antagonist of IL-1 and/or IL-1R function and antagonist(s) of one or more interleukin cytokines. Exemplary cytokines include, but are not limited to, IL-2, IL-4, IL-5, IL-6, IL-8, IL-12, IL-17, IL-18, and IL-23. In another embodiment, the composition comprises an antagonist of IL-1 and/or IL-1R function and antagonist(s) of one or more member(s) of the vascular epithelial growth factor (VEGF) family composed of growth factors and receptors (VEGFR). Exemplary members include, but are not limited to, VEGF-A, VEGF-C, VEGFR-2, and VEGFR-3. In another embodiment, the composition comprises an antagonist of IL-1 and/or IL-1R function and an antagonist of

interferon-gamma. In another embodiment, the composition comprises an antagonist of IL-1 and/or IL-1R function and antagonist(s) of one or more chemokines and their receptors. Exemplary chemokines and receptors comprised by the composition of this embodiment include, but are not limited to, chemokine (C-C motif) receptor 1 (CCR1), chemokine (C-C motif) receptor 2 (CCR2), chemokine (C-C motif) receptor 5 (CCR5), chemokine (C-C motif) receptor 7 (CCR7), and chemokine (C-X-C motif) receptor 3 (CXCR3).

[27] In embodiments wherein the composition comprises an antagonist of IL-1 and/or IL-1R function and antagonist(s) of one or more inflammatory species, the respective doses of the IL-1 antagonist to the other inflammatory antagonist(s) is a ratio between 1:10 and 10:1 (mass/weight). Alternatively, the ratio is 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, or 9:1.

[28] The invention also comprises a contact lens device consisting of a composition that inhibits an activity of an inflammatory interleukin-1 cytokine and a pharmaceutically compatible polymer. This composition also comprises a combination of antagonists of IL-1 or IL-1R function as well as antagonists of other inflammatory agents. For example, the composition is incorporated into or coated onto said lens. The composition is either chemically bound or physically entrapped by the contact lens polymer. The contact lens is either hydrophobic or hydrophilic.

[29] The invention comprises a drug-delivery device consisting of a composition that inhibits an activity of an inflammatory interleukin-1 cytokine and a pharmaceutically compatible polymer. This composition also comprises a combination of antagonists of IL-1 or IL-1R function as well as antagonists of other inflammatory agents. For example, the composition is incorporated into or coated onto said polymer. The composition is either chemically bound or physically entrapped by the polymer. The polymer is either hydrophobic or hydrophilic. The polymer device comprises multiple physical arrangements. Exemplary physical forms of the polymer device include, but are not limited to, a film, a scaffold, a chamber, a sphere, a microsphere, a stent, or other structure. The polymer device has internal and external surfaces. The device has one or more internal chambers. These chambers contain one or more compositions. The device contains polymers of one or more chemically-differentiable monomers. The subunits or monomers of the device polymerize *in vitro* or *in vivo*.

[30] Exemplary mucoadhesive polyanionic natural or semi-synthethic polymers from which the device is formed include, but are not limited to, polygalacturonic acid, hyaluronic acid, carboxymethylamylose, carboxymethylchitin, chondroitin sulfate, heparin sulfate, and mesoglycan. In one embodiment, the device comprises a biocompatible polymer matrix that may optionally be biodegradable in whole or in part. A hydrogel is one example of a suitable polymer matrix material. Examples of materials which can form hydrogels include polylactic acid, polyglycolic acid, PLGA polymers, alginates and alginate derivatives, gelatin, collagen, agarose, natural and synthetic polysaccharides, polyamino acids such as polypeptides particularly poly(lysine), polyesters such as polyhydroxybutyrate and poly-.epsilon.-caprolactone, polyanhydrides; polyphosphazines, poly(vinyl alcohols), poly(alkylene oxides) particularly poly(ethylene oxides), poly(allylamines)(PAM), poly(acrylates), modified styrene polymers such as poly(4-aminomethylstyrene), pluronic polyols, polyoxamers, poly(uronic acids), poly(vinylpyrrolidone) and copolymers of the above, including graft copolymers. In another embodiment, the scaffolds may be fabricated from a variety of synthetic polymers and naturally-occurring polymers such as, but not limited to, collagen, fibrin, hyaluronic acid, agarose, and laminin-rich gels.

[31] One preferred material for the hydrogel is alginate or modified alginate material. Alginate molecules are comprised of (1-4)-linked β-D-mannuronic acid (M units) and α L-guluronic acid (G units) monomers which vary in proportion and sequential distribution along the polymer chain. Alginate polysaccharides are polyelectrolyte systems which have a strong affinity for divalent cations (e.g. Ca^{+2}, Mg^{+2}, Ba^{+2}) and form stable hydrogels when exposed to these molecules. See Martinsen A., et al., Biotech. & Bioeng., 33 (1989) 79-89.

[32] An embodiment of the invention utilizes an alginate or other polysaccharide of a lower molecular weight, preferably of size which, after dissolution, is at the renal threshold for clearance by humans. Polymeric devices are located topically or subcutaneously, though very superficially, wherein either a composition chemically bound or physically entrapped by the polymeric device or the device itself, degrades and must be cleared from the body. For a biodegradable polymeric device, it is preferred that the alginate or polysaccharide is reduced to a molecular weight of 1000 to 80,000 daltons, more preferably 1000 to 60,000 daltons, particularly preferably 1000 to 50,000 daltons. It is also useful to use an alginate material of high guluronate

content since the guluronate units, as opposed to the mannuronate units, provide sites for ionic crosslinking through divalent cations to gel the polymer.

[33] Internal and external surfaces optionally contain pores. Pores are either created prior to administration into a subject or result from the inclusion of pore-forming agents within the device that perforate surfaces upon administration to a subject. Exemplary pore forming agents include, but are not limited to, water soluble compounds such as inorganic salts and sugars. Pore forming agents are added as particulates and comprise between one and thirty percent (weight/weight of polymer). Pore size is sufficient for diffusion of proteins but not large enough cell migration into or out of the device.

[34] The device is administered topically, subconjuntively, or in the episcleral space, subcutaneously, or intraductally. Specifically, the device is placed on or just below the surface if an ocular or adnexal tissue. Alternatively, the device is placed inside a tear duct or gland. The composition incorporated into or onto the polymer is released or diffuses from the device.

[35] The invention comprises a method of contacting a composition, with means to inhibit IL-1R activity, to an ocular or adnexal tissue surface of a subject who presents symptoms or associated conditions of posterior blepharitis. Unlike all other treatments for this condition, this method comprises a composition that is topically administered to the subject and affects local disease mechanisms without the side effects present with systemically administered treatments. The composition is not only effective immediately, but also safe for long-term administration.

[36] The invention comprises a method of treating non-infectious eye disease, wherein a composition containing an inhibitor of IL-1 or IL-1R function alleviates, prevents, or attenuates a symptom, cause, or mechanism of said disease by contacting said composition to the ocular surface of an affected subject. Exemplary disease mechanisms comprise inflammation, hyperplasia, neovascularization, leukocyte recruitment, or cytokine production within superficial eye structures and those structures juxtaposed to the ocular surface. For instance, non-infectious eye disease is caused by obstruction, thickening, inflammation, neovascularization, or atrophy of the meibomian glands. Alternatively, non-infectious eye disease is caused by damage to structures other than the meibomian glands. Exemplary alternative causes include, but are not limited to, oily tear film, papillary hypertrophy of the tarsal conjunctiva, corneal punctate epitheliopathy, vernal keratoconjunctivitis, atopic keratocojunctivitis, chemical burn, trachoma,

pterygium, pemphigoid, corneal angiogenesis(growth of new blood vessels), psoriasis, icthyosis, erythema mutiforme, anhydrotic ectodermal dysplasia, systemic retinoid therapy, or exposure to polychlorinated byphenols. Finally, non-infectious eye disease can also result from a deficient tear lipid layer, an increase in tear evaporation, or the occurrence of an evaporative dry eye. The methods treat non-infectious eye disease that is or is not coincident with the presentation of dermatoses comprising acne rosacea, seborrhoeic dermatitis, or atopic dermatitis. Furthermore, methods are applicable to treat a primary or secondary non-infectious eye disease that is coincident with chalazia, pannus, phlyctenules, recurrent conjunctivitis, ocular surface damage, ocular rosacea, corneal ulceration, corneal perforation or secondary complications of ocular infection.

[37] The methods described herein are not intended to treat eye disease that results from an immune response that consequently arises following the transplantation of foreign tissue onto or into an ocular or adnexal tissue. For instance, inflammatory responses occur following host rejection of corneal transplant or as a consequence of infection following surgical procedures. The instant application is not intended to treat eye conditions that result directly from tissue rejection or infectious disease. However, immune responses to foreign tissues or to infectious agents can lead to protean secondary complications, such as growth of blood or lymph vessels, or overexpression of molecules that cause tissue injury; in such cases the methods described in the present application are useful as a treatment for reducing inflammation associated with such secondary complications. Furthermore, the methods and devises comprising the instant application are not intended to treat conditions arising from autoimmune responses, e.g. immune responses raised against healthy host tissues.

[38] In a preferred embodiment, the non-infectious eye disease comprises blepharitis and/or posterior blepharitis that is or is not coincident with inflammation of the posterior lid margin, inflammation of the ocular surface, burning, irritation, or patient discomfort. Alternatively, the present invention is intended to treat blepharitis that is coincident with meibomian gland dysfunction.

[39] The methods alleviate symptoms of non-infectious eye disease. Exemplary symptoms include, but are not limited to, dryness, discomfort, burning, itching, irritation, inflammation, skin abnormalities surrounding the eye, photophobia, blurred vision, and contact lens intolerance.

[40] The present invention comprises a composition with variable physical and chemical forms; however, the composition is topically administered and contacts an ocular or adnexal tissue directly. The composition is administered as a solid, a paste, an ointment, a gel, a liquid, an aerosol, a mist, a polymer, a film, an emulsion, or a suspension. Furthermore, the composition is incorporated into or coated onto a contact lens, from which one or more molecules diffuse away from the lens or are released in a temporally-controlled manner. In this embodiment, the contact lens composition either remains on the ocular surface, e.g. if the lens is required for vision correction, or the contact lens dissolves as a function of time simultaneously releasing the composition into closely juxtaposed tissues.

[41] In one preferred embodiment, the present invention comprises 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.

[42] 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.

[43] The composition comprises 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 comprises 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.

[44] The composition comprises a molecule with means to inhibit IL-1α- or IL-β-mediated modulation of matrix metalloproteinase (MMP) overexpression, which degrades collagen matrices within tissues and retards wound healing.

[45] In another preferred embodiment, the composition comprises 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 ocular or lid surface. 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.

[46] Affected subjects to which this invention is administered are identified by a variety of methods. The following examinations are used individually or combinatorially to assess the presence or absence of non-infectious eye disease (for explanation of examinations, see Examples). Subjects are identified by a break-up time of less than 10 seconds following a standard Tear Film Break-up Time (TFBT) test. Subjects are identified by a significant corneal fluorescein staining of tear film and/or conjunctival lissamine green or rose bengal staining. Subjects are identified by a result of 10mm or less for the Schrimer test with or without anesthesia. Subjects are identified by significantly viscous tear excreta and/or a decrease in the number of meibomian glands or meibomian gland orifices capable of excreting tears. Subjects are identified by shades of red discoloration of the lid margin, palpebral conjunctiva, and/or bulbar conjunctiva indicating increasing extreme vascular injection (erythema). Subjects are also classified as presenting increasingly severe non-infectious eye disease with the increasing abundance and severity of the above factors.

[47] The compositions and methods provided herein are used modify intraocular pressure. In one aspect of the invention, the compositions and methods provided herein are used to decrease intraocular pressure. Inhibitors or antagonists of IL-1 cytokines and/ or IL-1 receptors are used alone or in combination with other compounds to modify intraocular pressure. In a preferred embodiment of the invention, inhibitors or antagonists of IL-1 cytokines and/ or IL-1 receptors are used alone or in combination with other compounds to decrease intraocular pressure. Alternatively, or in addition, inhibitors or antagonists of IL-1 cytokines and/ or IL-1 receptors are used alone or in combination with other compounds to treat ocular hypertension.

[48] Exemplary compounds to be used in combination with IL-1 cytokines and/ or IL-1 receptors include, but are not limited to, prostaglandin analogs (such as latanoprost (Xalatan), bimatoprost (Lumigan) and travoprost (Travatan) which increase uveoscleral or trabecular outflow of aqueous humor); topical beta-adrenergic receptor antagonists (such as timolol, levobunolol (Betagan), and betaxolol, which decrease aqueous humor production by the ciliary body); Alpha2-adrenergic agonists (such as brimonidine (Alphagan), which work by a dual mechanism, decreasing aqueous production and increasing uveo-scleral outflow); less-selective sympathomimetics (such as epinephrine and dipivefrin (Propine), which increase outflow of aqueous humor through trabecular meshwork and possibly through uveoscleral outflow pathway, probably by a beta2-agonist action); miotic agents (parasympathomimetics) (such as pilocarpine, which work by contraction of the ciliary muscle, tightening the trabecular meshwork and allowing increased outflow of the aqueous humour); carbonic anhydrase inhibitors (such as dorzolamide (Trusopt), brinzolamide (Azopt), acetazolamide (Diamox), which lower secretion of aqueous humor by inhibiting carbonic anhydrase in the ciliary body); physostigmine which is also used to treat glaucoma and delayed gastric emptying; fish oil; omega 3 fatty acids, bilberries, vitamin E, cannabinoids, carnitine, coenzyme Q10, curcurmin, Salvia miltiorrhiza, dark chocolate, erythropoietin, folic acid, Ginkgo biloba, Ginseng, L-glutathione, grape seed extract, green tea, magnesium, melatonin, methylcobalamin, N-acetyl-L cysteine, pycnogenols, resveratrol, quercetin, and fludrocortisone.

[49] The invention also provides compositions and methods for treating individuals or subjects with ocular hypertension including administrating to these subjects a composition comprising an IL-1 or IL-1R inhibitor or antagonist. In one aspect of the invention, the IL-1 or IL-1R inhibitor or antagonist is administered topically to the ocular surface as a liquid. In

another aspect of the invention, the IL-1 or IL-1R inhibitor or antagonist is administered intraocularly by injection.

[50] The invention also provides compositions and methods for preventing glaucoma in individuals or subjects with ocular hypertension including administrating to these subjects a composition comprising an IL-1 or IL-1R inhibitor or antagonist. In one aspect of the invention, the IL-1 or IL-1R inhibitor or antagonist is administered topically to the ocular surface as a liquid. In another aspect of the invention, the IL-1 or IL-1R inhibitor or antagonist is administered intraocularly by injection.

[51] The invention provides a method for reducing intraocular pressure, including identifying a subject suffering from or at risk of a condition associated with above-normal intra-ocular pressure and locally administering to the subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine. In one preferred aspect of the invention, the condition is glaucoma.

[52] In one aspect of the invention, subjects are identified by measuring their intraocular pressure and determining if the measured intraocular pressure is elevated above normal levels. As used herein, the term "normal level" is meant to describe value within an acceptable range of values that one of ordinary skill in the art and/or a medical professional would expect a healthy subject of similar physical characteristics and medical history to have. For example, normal intraocular pressure (IOP) is defined as IOP in the range of 10 mmHg to 21 mmHg.

[53] In another aspect of the invention, subjects are identified as those individuals who are at risk for developing elevated intraocular pressure based upon non-limiting factors such as medical history (for instance, diabetes), side effects of medications, lifestyle and/or diet, medical intervention (such as surgery to the eye), trauma/injury, hormone changes, and aging. Compositions of the invention are administered to these subjects for preventative means.

[54] 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, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized.

[55] 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

[56] **Figure 1** is the Ocular Surface Disease Index (OSDI) 12-item questionnaire.

[57] **Figure 2** the Oxford Schema for grading corneal and conjunctival staining.

[58] **Figure 3** is a graph representing the effect of IL-1a on intraocular pressure (IOP).

[59] **Figure 4** is a schematic representation of signaling pathways that are transduced from the IL-1R and the downstream effectors involved in carrying these intracellular signals (drawing reproduced from BioCarta website).

[60] **Figure 5** is a questionnaire given to subjects of a study to diagnose Meibomian Gland Dysfunction (Posterior Blepharitis).

[61] **Figure 6** is a flow diagram showing the sequence of clinical tests performed on study subjects during the screening process described in Example 8.

DETAILED DESCRIPTION

Posterior Blepharitis

[62] Posterior blepharitis is a common chronic eyelid condition that is described as generalized inflammation of the posterior lid margin and associated with inflammation of the ocular surface and with symptoms of burning, irritation, and discomfort. Posterior blepharitis is associated with various disorders of the meibomian glands, known collectively as meibomian gland dysfunction (MGD). It is associated either with obstruction and inflammation of the meibomian glands or, less commonly, atrophy of the meibomian glands (Foulks, G. et al. 2003. Ocul Surf. 107-26; Bron, A.J. et al. 2004. Ocul Surf. 2:149-65).

[63] Clinically, MGD often presents with inspissated meibomian glands, oily tear film, as well as inflammation and vascularization of the meibomian gland orifices. Papillary hypertrophy of the tarsal conjunctiva and corneal punctate epitheliopathy are often present, and there are prominent associations with dermatoses, such as acne rosacea, seborrhoeic dermatitis, and atopic dermatitis. Other causes and associations of MGD are: vernal keratoconjunctivitis, atopic keratoconjunctivitis, chemical burns, trachoma, pemphigoid, psoriasis, icthyosis, erythema multiforme, anhydrotic ectodermal dysplasia, and systemic retinoid therapy. Additionally, exposure to polychlorinated biphenyls, through ingestion of contaminated cooking oils, causes a chronic form of MGD with gross and extensive acneiform skin changes (Fu, Y.A. 1984. Am J Ind Med. 5:127-32).

[64] MGD of sufficient extent and degree is associated with a deficient tear lipid layer, an increase in tear evaporation, and the occurrence of an evaporative dry eye. In fact MGD is considered to be the most common cause of evaporative dry eye (Foulks, G. et al. 2003. Ocul Surf. 107-26). Individuals with MGD often complain of significant discomfort, including burning, itching, irritation, and photophobia. They may also have other associated symptoms of dry eye and may be plagued by blurred vision, gradual contact lens intolerance. Furthermore, these patients may become functionally handicapped by the negative impact of dry eye on their crucial daily activities such as working, reading, using computer, and driving (Goto, E. et al. 2002. Am J Opthalmol. 133:181-186; Miljanovic, B. et al. 2007. Am J Opthalmol. 143: 409-15).

[65] In addition to dry eye, other sequelae of MGD that confront the ophthalmologist include chalazia, pannus, phlyctenules, and recurrent conjunctivitis which increase risk of ocular surface damage, ocular infection, corneal ulceration, and perforation.

[66] Despite the high incidence of posterior blepharitis, there is currently no consistently effective treatment for this condition and it still remains a therapeutic challenge. Posterior blepharitis has traditionally been managed with eyelid hygiene, topical antibiotics (erythromycin or bacitracin ointments), oral tetracyclines (tetracycline, doxycycline, or minocycline) and corticosteroids which are often time consuming, frustrating, and frequently ineffective or variably effective.

[67] The current treatments for posterior blepharitis are limited, in part, by their inability to target the underlying pathophysiologic processes. There is ample evidence that posterior blepharitis is the result of an underlying cytokine and inflammatory-mediated process affecting

both the meibomian glands and the ocular surface (Kocak-Altintas, A.G. et al. 2003. Eur J Opthalmol. 13:351-359; McCulley, J.P. et al. 2000. Cornea. 19:650-658). In an experimental blepharoconjunctivitis, it has been shown that T-cells are the prime orchestrator driving the infiltration of other inflammatory cells into the conjunctiva, as well as the upregulation of chemokines (Fukushima, A. et al. 2003. Invest. Opthalmol. Vis. Sci. 44:4366-4374).

[68] In ocular rosacea which belongs to the large pathologic group of blepharitis and MGD, inflammation of the ocular surface was clearly demonstrated with an increase of inflammatory mediators in tears such as interleukin (IL)-1α (Barton, K. et al. 1997. Opthalmology. 104:1868-1874). Flow cytometry and impression cytology of conjunctival epithelium in ocular rosacea has demonstrated a significantly higher level of intercellular adhesion molecule-1 (ICAM-1) which is known to play a significant role in inflammation associated with dry eye disease. This expression of ICAM-1 could be due to the liberation of one or more pro-inflammatory cytokines such as IL-1β or interferon-γ (Pisella, P.J. et al. 2000. Opthalmology. 107:1841-9).

[69] Importance of inflammation in the pathogenesis of posterior blepharitis is underscored by reports that the signs and symptoms of MGD markedly improve with anti-inflammatory therapies such as topical steroids (Marsh, P. et al. 1999. Opthalmology.106:811-816).

[70] Systemically administered tetracycline antibiotics have long been recognized as effective therapies for ocular surface inflammatory diseases. The semisynthetic tetracycline, doxycycline, has been reported to successfully treat the common dry eye condition acne rosacea. One of the mechanisms of action of doxycycline in MGD and dry eye may be the downregulation of the IL-1–mediated inflammatory cascade in the corneal epithelium (Solomon, A. et al. 2000. Invent. Opthalmol. Vis. Sci. 41:2544-57).

[71] In addition, findings from several studies indicate that MGD is also associated with aqueous deficiency dry eye patients, especially those with Sjogren syndrome (SS) (McCulley, J.P. et al.1977. A, J Opthalmol. 84:788-93; Shimazaki, J. et al. 1998.Opthalmology. 105: 1485-1488). In these studies, at least 35% of patients with aqueous tear deficiency had MGD. Classically, SS affects the exocrine glands, not the sebaceous glands such as the meibomian glands. Underlying inflammation as well as desiccation and keratinization of ocular surface epithelia occurs in chronic dry eye disease and plays a role in pathogenesis of MGD.

[72] Consistent with the concept that inflammation is a key feature in the pathophysiology of dry eye syndrome is the finding that both aqueous tear deficiency and meibomian gland disease

are effectively treated with the corticosteroid methylprednisolone (Marsh, P. et al. 1999. Opthalmology. 107:967-74). Unfortunately the long-term use of topical corticosteroids is limited by potential sight-threatening side effects, such as glaucoma and cataracts. Therefore, there is a clinical need for nontoxic steroid-sparing anti-inflammatory therapies that target the underlying inflammatory environment of the ocular surface in this common condition.

[73] Based on the concept that inflammation is a key component of the pathogenesis of MGD and dry eye, therapies targeting the underlying inflammatory environment of the ocular surface represent a major improvement in the management of these conditions and will have a major clinical impact. Given the facts that IL-1–mediated inflammatory activities play a critical role on the ocular surface in patients with MGD and dry eye, therefore, local blockade of IL-1 activity by IL-1Ra, is used to reduce one or more symptoms of dry eye syndrome.

Ocular and Adnexal Tissues:

[74] Ocular tissues or compartments that contact the compositions comprised by the present invention include, but are not limited to, the cornea, aqueous humor, iris, and sclera. The term "adnexal" is defined in general terms as the appendages of an organ. In the present invention, adnexal defines a number of tissues or surfaces that are in immediate contact with the ocular surface but are not, by definition, comprised by the ocular surface. Exemplary adnexal tissues include, but are not limited to, the eyelids, lacrimal glands, and extraocular muscles. Topical administration of the presently invented compositions contact the following tissues and structures within the eyelid: skin, subcutaneous tissue, orbicularis oculi, orbital septum, tarsal plates, palpebral conjuntiva, and meibomian glands. The adnexal tissues comprise all subdivisions of the lacrimal glands, including the orbital and palpebral portions, as well as all tissues contacted by these glands. Extraocular muscles belonging to this category of adnexal tissues include, but are not limited to, the superior and inferior rectus, lateral and medial rectus, and superior and inferior oblique muscles. Compositions comprised by the present invention are applied topically and contact these tissues either alone, or in combination with ocular tissues.

Intraocular Pressure

[75] Intraocular pressure is maintained by the liquid aqueous humor, which is produced by the ciliary body of the eye. Aqueous humor normally does not go into the posterior segment of the eye; it is kept out of this area by the lens and the Zonule of Zinn. Instead, it stays only in the anterior segment, which is divided into the anterior and posterior chambers. While the anterior

and posterior *chambers* are very similarly named to the anterior and posterior *segments*, they are not synonymous. The anterior and posterior chambers are both parts of the anterior segment.

[76] When the ciliary bodies produce the aqueous humor, it first flows into the posterior chamber (bounded by the lens and the iris). It then flows through the pupil of the iris into the anterior chamber (bounded by the iris and the cornea). From here, it flows through a structure known as the trabecular meshwork to enter the normal body circulation. Thus, the two main mechanisms of ocular hypertension are an increased production of aqueous humor, or a decreased outflow of aqueous humor.

[77] Ocular hypertension (OHT) is intraocular pressure higher than normal in the absence of optic nerve damage or visual field loss. Current consensus in ophthalmology defines normal intraocular pressure (IOP) as that between 10 mmHg and 21 mmHg. Intraocular pressure is measured with a tonometer. Elevated IOP is the most important risk factor for glaucoma, so those with ocular hypertension are frequently considered to have a greater chance of developing the condition. Intraocular pressure can increase when a patient lies down. There is evidence that some glaucoma patients (e.g., normal tension glaucoma patients) with normal IOP while sitting or standing may have intraocular pressure that is elevated enough to cause problems when they are lying down.

[78] Differences in pressure between the two eyes is often clinically significant, and potentially associated with certain types of glaucoma, as well as iritis or retinal detachment.

[79] Because of the effect of corneal thickness and rigidity on measured value of intraocular pressure, some forms of refractive surgery (such as photorefractive keratectomy) can cause traditional intraocular pressure measurements to appear normal when in fact the pressure may be abnormally high.

[80] Intraocular pressure may become elevated due to anatomical problems, inflammation of the eye, genetic factors, as a side-effect from medication, or during exercise. Intraocular pressure usually increases with age and is genetically influenced.
Hypotony, or ocular hypotony, is typically defined as intraocular pressure equal to or less than 5 mmHg. Such low intraocular pressure could indicate fluid leakage and deflation of the eyeball.

Glaucoma

[81] Glaucoma is a leading cause of irreversible blindness. A primary risk factor for glaucoma is elevated intraocular pressure (IOP), which can contribute to significant optic nerve damage and vision loss. Elevated IOP due to reduction in aqueous outflow facility is a major causal risk factor. The main aqueous outflow pathway of the eye consists of a series of endothelial-cell–lined channels in the angle of the anterior chamber comprising the trabecular meshwork (TM), Schlemm's canal, the collector channels and the episcleral venous system.

[82] Glaucoma is a group of diseases of the optic nerve involving loss of retinal ganglion cells in a characteristic pattern of optic neuropathy. Although raised intraocular pressure is a significant risk factor for developing glaucoma, there is no set threshold for intraocular pressure that causes glaucoma. Untreated glaucoma leads to permanent damage of the optic nerve and resultant visual field loss, which can progress to blindness. Loss of visual field often occurs gradually over a long time and may only be recognized when it is already quite advanced. Once lost, this damaged visual field can never be recovered. Worldwide, it is the second leading cause of blindness. Glaucoma affects one in two hundred people aged fifty and younger, and one in ten over the age of eighty.

[83] Ocular hypertension is the largest risk factor in most glaucomas. Though, in some populations only 50% of patients with primary open angle glaucoma have elevated ocular pressure. Diabetics and those of African descent are three times more likely to develop primary open angle glaucoma. Higher age, thinner corneal thickness, and myopia are also risk factors for primary open angle glaucoma. People with a family history of glaucoma have about a six percent chance of developing glaucoma. Asians are prone to develop angle-closure glaucoma, and Inuit have a twenty to forty times higher risk than Caucasians of developing primary angle closure glaucoma. Women are three times more likely than men to develop acute angle-closure glaucoma due to their shallower anterior chambers. Use of steroids can also cause glaucoma.

[84] Primary open angle glaucoma (POAG) has been found to be associated with mutations in genes at several loci. Normal tension glaucoma, which comprises one third of POAG, is associated with genetic mutations.

[85] There is increasing evidence of ocular blood flow to be involved in the pathogenesis of glaucoma. Current data indicate that fluctuations in blood flow are more harmful in

glaucomatous optic neuropathy than steady reductions. Unstable blood pressure and dips are linked to optic nerve head damage and correlate with visual field deterioration.

[86] A number of studies also suggest that there is a correlation, not necessarily causal, between glaucoma and systemic hypertension (i.e. high blood pressure). In normal tension glaucoma, nocturnal hypotension may play a significant role. On the other hand there is no clear evidence that vitamin deficiencies cause glaucoma in humans, nor that oral vitamin supplementation is useful in glaucoma treatment.

[87] Various rare congenital/genetic eye malformations are associated with glaucoma. Occasionally, failure of the normal third trimester gestational atrophy of the hyaloid canal and the tunica vasculosa lentis is associated with other anomalies. Angle closure induced ocular hypertension and glaucomatous optic neuropathy may also occur with these anomalies. These rare developmental causes of glaucoma are modeled in mice.

[88] Only a few glaucomas are associated with visible cellular inflammation in the ocular compartments; however, Interleukin-1 (IL-1) is consistently up-regulated by glaucomatous TM cells and acts as a key factor in accelerated TM cell injury. This condition is mediated by both IL-1 effect on the TM cells functioning as well as their expression of adhesion factors that can affect outflow facility. The net effect is that IL-1 can compromises the function of the trabecular meshwork, causing reduced outflow facility in the open angle glaucoma. Interleukin-1 receptor antagonist (IL-1Ra) is a naturally occurring IL-1 isoform that with high-affinity binds to the IL-1 receptors and blocks its effects. Therefore, topical application of IL-1Ra, such as human recombinant forms (anakinra/Kineret) suppresses IL-1-mediated cell injury in TM, enhances outflow facility, and reduces IOP in glaucomatous eyes.

[89] This mechanism of action is in contrast with the other views that IL-1 itself increases matrix metalloproteinase expression in the TM and increases outflow facility. Therefore, others believed that inhibition of action of IL-1 by an IL-1 neutralizing antibody or with IL-1 receptor antagonist causes reduced outflow facility in trabecular meshwork.

Interleukin-1 (IL-1):

[90] 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).

[91] The IL-1 cytokines play an important role in the regulation of inflammation and wound healing in the corneal and ocular surface diseases (Fabre, E.J. et al. 1991. Curr Eye Res. 10:585-592; Rosenbaum, J.T. et al. 1995. Invest Opthalmol Vis Sci. 36: 2151-2155). Both IL-1α and IL-1ß have been found to modulate matrix metalloproteinase (MMP) expression by corneal stromal fibroblasts (Fini, M.E. et al. 1990. Invest Opthalmol Vis Sci. 31:1779-1788). Increased levels of IL-1α and IL-1ß have been shown in patients with Sjögren syndrome and ocular rosacea (Pflugfelder, S.C. et al. 1999. Curr Eye Res. 19:201-211; Solomon, A. et al. 2001. Invest Opthalmol Vis Sci. 42:2283-2292). Levels of proinflammatory forms of IL-1 are directly correlated with the intensity of corneal fluorescein staining and are inversely correlated with conjunctival goblet cell density. In both types of dry eye syndrome, evaporative and aqueous deficiency, as tear clearance from the ocular surface decreases, the concentrations of both isoforms of the proinflammatory cytokine IL-1 increase in the tear fluid (Solomon, A. et al. 2001. Invest Opthalmol Vis Sci. 42:2283-2292). The results of a study on the effects of doxycycline on the expression patterns of the IL-1 gene family in the human limbal epithelium in response to a strong inflammatory stimulus, have demonstrated an inhibitory effect of doxycycline on the expression of the inflammatory cytokine IL-1β, with a concomitant upregulation of the anti-inflammatory IL-1Ra (Solomon, A. et al. 2000. Invest Opthalmol Vis Sci. 41:2544-57). These results imply that some of the clinically proven benefits of tetracycline compounds (tetracycline, doxycycline, and minocycline) in treating the ocular surface disease of MGD and dry eye may be mediated through their regulatory effects on the synthesis, processing, or release of IL-1.

[92] IL-1 induces ocular surface disease, e.g., the chronic subclinical ocular surface inflammation of MGD and dry eye. 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).

[93] 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.

[94] 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.)

accaggcaacaccattgaaggctcatatgtaaaaatccatgccttcctttctcccaatctccattcccaa
acttagccactggcttctggctgaggccttacgcatacctcccggggcttgcacacaccttcttctacag
aagacacaccttgggcatatcctacagaagaccaggcttctctctggtccttggtagagggctactttac
tgtaacagggccagggtggagagttctctcctgaagctccatcccctctataggaaatgtgttgacaata
ttcagaagagtaagaggatcaagacttctttgtgctcaaataccactgttctcttctctaccctgcccta
accaggagcttgtcaccccaaactctgaggtgatttatgccttaatcaagcaaacttccctcttcagaaa
agatggctcattttccctcaaaagttgccaggagctgccaagtattctgccaattcaccctggagcacaa
tcaacaaattcagccagaacacaactacagctactattagaactattattattaataaattcctctccaa
atctagcccctgacttcggatttcacgatttctcccttcctcctagaaacttgataagtttcccgcgct
tccctttttctaagactacatgtttgtcatcttataaagcaaaggggtgaataaatgaaccaaatcaata
acttctggaatatctgcaaacaacaataatatcagctatgccatctttcactattttagccagtatcgag
ttgaatgaacatagaaaaatacaaaactgaattcttccctgtaaattccccgttttgacgacgcacttgt
agccacgtagccacgcctacttaagacaattacaaaaggcgaagaagactgactcaggcttaagctgcca
gccagagagggagtcatttcattggcgtttgagtcagcaaagaagtcaag**ATG**gccaaagttccagacat
gtttgaagacctgaagaactgttacagtgaaaatgaagaagacagttcctccattgatcatctgtctctg
aatcagaaatccttctatcatgtaagctatggcccactccatgaaggctgcatggatcaatctgtgtctc
tgagtatctctgaaacctctaaaacatccaagcttaccttcaaggagagcatggtggtagtagcaaccaa
cgggaaggttctgaagaagagacggttgagtttaagccaatccatcactgatgatgacctggaggccatc
gccaatgactcagaggaagaaatcatcaagcctaggtcagcacctttagcttcctgagcaatgtgaaat

acaactttatgaggatcatcaaatacgaattcatcctgaatgacgccctcaatcaaagtataattcgagc
caatgatcagtacctcacggctgctgcattacataatctggatgaagcagtgaaatttgacatgggtgct
tataagtcatcaaaggatgatgctaaaattaccgtgattctaagaatctcaaaaactcaattgtatgtga
ctgcccaagatgaagaccaaccagtgctgctgaaggagatgcctgagatacccaaaaccatcacaggtag
tgagaccaacctcctcttcttctgggaaactcacggcactaagaactatttcacatcagttgcccatcca
aacttgtttattgccacaaagcaagactactgggtgtgcttggcaggggggccaccctctatcactgact
ttcagatactggaaaaccaggcgtaggtctggagtctcacttgtctcacttgtgcagtgttgacagttca
tatgtaccatgtacatgaagaagctaaatcctttactgttagtcatttgctgagcatgtactgagccttg
taattctaaatgaatgtttacactctttgtaagagtggaaccaacactaacatataatgttgttatttaa
agaacaccctatattttgcatagtaccaatcattttaattattattcttcataacaattttaggaggacc
agagctactgactatggctaccaaaaagactctacccatattacagatgggcaaattaaggcataagaaa
actaagaaatatgcacaatagcagttgaaacaagaagccacagacctaggatttcatgatttcatttcaa
ctgtttgccttctacttttaagttgctgatgaactcttaatcaaatagcataagtttctgggacctcagt
tttatcattttcaaaatggagggaataatacctaagccttcctgccgcaacagttttttatgctaatcag
ggaggtcattttggtaaaatacttcttgaagccgagcctcaagatgaaggcaaagcacgaaatgttattt
tttaattattatttatatatgtatttataaatatatttaagataattataatatactatatttatgggaa
ccccttcatcctctgagtgtgaccaggcatcctccacaatagcagacagtgttttctgggataagtaagt
ttgatttcattaatacagggcattttggtccaagttgtgcttatcccatagccaggaaactctgcattct
agtacttgggagacctgtaatcatataataaatgtacattaattaccttgagccagtaattggtccgatc
tttgactcttttgccattaaacttacctgggcattcttgtttcaattccacctgcaatcaagtcctacaa
gctaaaattagatgaactcaactttgacaaccatgagaccactgttatcaaaactttcttttctggaatg
taatcaatgtttcttctaggttctaaaaattgtgatcagaccataatgttacattattatcaacaatagt
gattgatagagtgttatcagtcataactaaataaagcttgcaacaaaattctctgacaaaaaaaaaaaaa
aaa.

[95] Human IL-1α is encoded by the following amino acid sequence (NCBI Accession No. NM_000575 and SEQ ID NO: 2):

MAKVPDMFEDLKNCYSENEEDSSSIDHLSLNQKSFYHVSYGPLHDSEEEIIKPRSAPFSFL
SNVKYNFMRIIKYEFILNDALNQSIIRANDQYLTAAALHNLDEAVKFDMGAYKSSKDDA
KITVILRISKTQLYVTAQDEDQPVLLKEMPEIPKTITGSETNLLFFWETHGTKNYFTSVAH
PNLFIATKQDYWVCLAGGPPSITDFQILENQA.

[96] Human IL-1β is encoded by the following mRNA sequence (NCBI Accession No. NM_000576 and SEQ ID NO: 3):

accaaacctcttcgaggcacaaggcacaacaggctgctctgggattctcttcagccaatcttcattgctc
aagtgtctgaagcagcc**ATG**gcagaagtacctgagctcgccagtgaaatgatggcttattacagtggcaa
tgaggatgacttgttctttgaagctgatggccctaaacagatgaagtgctccttccaggacctggacctc
tgccctctggatggcggcatccagctacgaatctccgaccaccactacagcaagggcttcaggcaggccg
cgtcagttgttgtggccatggacaagctgaggaagatgctggttccctgcccacagaccttccaggagaa
tgacctgagcaccttctttcccttcatctttgaagaagaacctatcttcttcgacacatgggataacgag
gcttatgtgcacgatgcacctgtacgatcactgaactgcacgctccgggactcacagcaaaaaagcttgg
tgatgtctggtccatatgaactgaaagctctccacctccagggacaggatatggagcaacaagtggtgtt
ctccatgtcctttgtacaaggagaagaaagtaatgacaaaatacctgtggccttgggcctcaaggaaaag
aatctgtacctgtcctgcgtgttgaaagatgataagcccactctacagctggagagtgtagatcccaaaa
attacccaaagaagaagatggaaaagcgatttgtcttcaacaagatagaaatcaataacaagctggaatt
tgagtctgcccagttccccaactggtacatcagcacctctcaagcagaaaacatgcccgtcttcctggga
gggaccaaaggcggccaggatataactgacttcaccatgcaatttgtgtcttcctaaagagagctgtacc
cagagagtcctgtgctgaatgtggactcaatccctagggctggcagaaagggaacagaaaggtttttgag
tacggctatagcctggactttcctgttgtctacaccaatgcccaactgcctgccttagggtagtgctaag
aggatctcctgtccatcagccaggacagtcagctctctcctttcagggccaatccccagccctttttgttg
agccaggcctctctcacctctcctactcacttaaagcccgcctgacagaaaccacggccacatttggttc
taagaaaccctctgtcattcgctcccacattctgatgagcaaccgcttccctatttatttatttatttgt
ttgtttgttttattcattggtctaatttattcaaaggggcaagaagtagcagtgtctgtaaaagagcct

agtttttaatagctatggaatcaattcaatttggactggtgtgctctctttaaatcaagtcctttaatta
agactgaaaatatataagctcagattatttaaatgggaatatttataaatgagcaaatatcatactgttc
aatggttctgaaataaacttcactgaag.

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

MAEVPELASEMMAYYSGNEDDLFFEADGPKQMKCSFQDLDLCPLDGGIQLRISDHHYS
KGFRQAASVVVAMDKLRKMLVPCPQTFQENDLSTFFPFIFEEEPIFFDTWDNEAYVHDA
PVRSLNCTLRDSQQKSLVMSGPYELKALHLQGQDMEQQVVFSMSFVQGEESNDKIPVA
LGLKEKNLYLSCVLKDDKPTLQLESVDPKNYPKKKMEKRFVFNKIEINNKLEFESAQFP
NWYISTSQAENMPVFLGGTKGGQDITDFTMQFVSS.

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

[98] 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, such as rheumatoid arthritis (Arend, W.P. 1993. Adv Immunol. 54: 167-223).

[99] Normal tear fluid has been found to contain high concentrations of IL-1Ra in concentrations 25,000 and 40,000 times greater than both proinflammatory forms of IL-1 (Solomon, A. et al. 2001. Invest Opthalmol Vis Sci. 42: 2283-2292). The high concentration of IL-1Ra in the tear fluid may be a natural homeostatic mechanism for preventing inappropriate activation of IL-1–mediated inflammatory events on the ocular surface (Dinarello, C.A. 1996. Blood. 15:2095-2147).

[100] An increased concentration of IL-1Ra has been detected in the tear fluid of patients with dry eye and in the conjunctival epithelium of patients with dry eye syndrome (Solomon, A. et al. 2001. Invest Opthalmol Vis Sci. 42: 2283-2292). Despite this increased level of expression, the ratio of IL-1Ra to proinflammatory forms IL-1 dry-eye was significantly lower than in normal subjects. Reports of placebo-controlled clinical trials in which IL-1Ra was administered to patients with rheumatoid arthritis have noted that increasing the ratio of IL-1Ra to the proinflammatory forms significantly improves clinical symptoms (Dinarello, C.A. 2000. N Engl J Med. 343:732-734).

[101] 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.

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

atttctttataaaccacaactctgggcccgcaatggcagtccactgccttgctgcagtcacaga**ATG**gaa
atctgcagaggcctccgcagtcacctaatcactctcctcctcttcctgttccattcagagacgatctgcc
gaccctctgggagaaaatccagcaagatgcaagccttcagaatctgggatgttaaccagaagaccttcta
tctgaggaacaaccaactagttgctggatacttgcaaggaccaaatgtcaatttagaagaaaagatagat
gtggtacccattgagcctcatgctctgttcttgggaatccatggagggaagatgtgcctgtcctgtgtca
agtctggtgatgagaccagactccagctggaggcagttaacatcactgacctgagcgagaacagaaagca
ggacaagcgcttcgccttcatccgctcagacagcggccccaccaccagttttgagtctgccgcctgcccc
ggttggttcctctgcacagcgatggaagctgaccagcccgtcagcctcaccaatatgcctgacgaaggcg
tcatggtcaccaaattctacttccaggaggacgagtagtactgcccaggcctgcctgttcccattcttgc
atggcaaggactgcagggactgccagtccccctgccccagggctcccggctatgggggcactgaggacca
gccattgaggggtggaccctcagaaggcgtcacaagaacctggtcacaggactctgcctcctcttcaact
gaccagcctccatgctgcctccagaatggtctttctaatgtgtgaatcagagcacagcagcccctgcaca
aagcccttccatgtcgcctctgcattcaggatcaaaccccgaccacctgcccaacctgctctcctcttgc
cactgcctcttcctccctcattccaccttcccatgccctggatccatcaggccacttgatgaccccaac
caagtggctcccacaccctgttttacaaaaaagaaaagaccagtccatgagggaggttttaagggtttg
tggaaaatgaaaattaggatttcatgatttttttttttcagtccccgtgaaggagagcccttcatttgga
gattatgttctttcggggagaggctgaggacttaaaatattcctgcatttgtgaaatgatggtgaaagta
agtggtagcttttcccttcttttttcttcttttttttgtgatgtcccaacttgtaaaaattaaaagttatgg
tactatgttagccccataatttttttttttccttttaaaacacttccataatctggactcctctgtccagg
cactgctgcccagcctccaagctccatctccactccagatttttttacagctgcctgcagtactttacctc
ctatcagaagtttctcagctcccaaggctctgagcaaatgtggctcctgggggttctttcttcctctgct
gaaggaataaattgctccttgacattgtagagcttctggcacttggagacttgtatgaaagatggctgtg
cctctgcctgtctcccccaccgggctgggagctctgcagagcaggaaacatgactcgtatatgtctcagg
tccctgcagggccaagcacctagcctcgctcttggcaggtactcagcgaatgaatgctgtatatgttggg
tgcaaagttccctacttcctgtgacttcagctctgttttacaataaaatcttgaaaatgcctaaaaaaaaa
aaaaaaaaaa.

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

MEICRGLRSHLITLLLFLFHSETICRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYL
QGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQD
KRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE.

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

gggcagctccaccctgggagggactgtggcccaggtactgcccgggtgctactttatgggcagcagctca
gttgagttagagtctggaagacctcagaagacctcctgtcctatgaggccctcccc**ATG**gctttagctga
cttgtatgaagaaggaggtggaggaggaggagaaggtgaagacaatgctgactcaaaggagacgatctgc
cgaccctctgggagaaaatccagcaagatgcaagccttcagaatctgggatgttaaccagaagaccttct
atctgaggaacaaccaactagttgctggatacttgcaaggaccaaatgtcaatttagaagaaaagataga
tgtggtacccattgagcctcatgctctgttcttgggaatccatggagggaagatgtgcctgtcctgtgtc

aagtctggtgatgagaccagactccagctggaggcagttaacatcactgacctgagcgagaacagaaagc
aggacaagcgcttcgccttcatccgctcagacagcggccccaccaccagttttgagtctgccgcctgccc
cggttggttcctctgcacagcgatggaagctgaccagcccgtcagcctcaccaatatgcctgacgaaggc
gtcatggtcaccaaattctacttccaggaggacgagtagtactgcccaggcctgcctgttcccattcttg
catggcaaggactgcagggactgccagtccccctgccccagggctcccggctatgggggcactgaggacc
agccattgaggggtggaccctcagaaggcgtcacaagaacctggtcacaggactctgcctcctcttcaac
tgaccagcctccatgctgcctccagaatggtctttctaatgtgtgaatcagagcacagcagcccctgcac
aaagcccttccatgtcgcctctgcattcaggatcaaaccccgaccacctgcccaacctgctctcctcttg
ccactgcctcttcctccctcattccaccttcccatgccctggatccatcaggccacttgatgacccccaa
ccaagtggctcccacaccctgttttacaaaaaagaaaagaccagtccatgagggaggtttttaagggttt
gtggaaaatgaaaattaggatttcatgatttttttttttcagtccccgtgaaggagagcccttcatttgg
agattatgttctttcggggagaggctgaggacttaaaatattcctgcatttgtgaaatgatggtgaaagt
aagtggtagcttttcccttcttttttcttcttttttttgtgatgtcccaacttgtaaaaattaaaagttatg
gtactatgttagccccataattttttttttcctttaaaacacttccataatctggactcctctgtccag
gcactgctgcccagcctccaagctccatctccactccagatttttacagctgcctgcagtactttacct
cctatcagaagtttctcagctcccaaggctctgagcaaatgtggctcctgggggttctttcttcctctgc
tgaaggaataaattgctccttgacattgtagagcttctggcacttggagacttgtatgaaagatggctgt
gcctctgcctgtctccccccaccgggctgggagctctgcagagcaggaaacatgactcgtatatgtctcag
gtccctgcagggccaagcacctagcctcgctcttggcaggtactcagcgaatgaatgctgtatatgttgg
gtgcaaagttccctacttcctgtgacttcagctctgttttacaataaaatcttgaaaatgcctaaaaaaa
aaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa.

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

MALADLYEEGGGGGGEGEDNADSKETICRPSGRKSSKMQAFRIWDVNQKTFYLRNNQ
LVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLS
ENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFY
FQEDE.

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

gggcagctccaccctgggagggactgtggcccaggtactgcccgggtgctactttatgggcagcagctca
gttgagttagagtctggaagacctcagaagacctcctgtcctatgaggccctcccc**ATG**gctttagagac
gatctgccgaccctctgggagaaaatccagcaagatgcaagccttcagaatctgggatgttaaccagaag
accttctatctgaggaacaaccaactagttgctggatacttgcaaggaccaaatgtcaatttagaagaaa
agatagatgtggtacccattgagcctcatgctctgttcttgggaatccatggagggaagatgtgcctgtc
ctgtgtcaagtctggtgatgagaccagactccagctggaggcagttaacatcactgacctgagcgagaac
agaaagcaggacaagcgcttcgccttcatccgctcagacagcggccccaccaccagttttgagtctgccg
cctgccccggttggttcctctgcacagcgatggaagctgaccagcccgtcagcctcaccaatatgcctga
cgaaggcgtcatggtcaccaaattctacttccaggaggacgagtagtactgcccaggcctgcctgttccc
attcttgcatggcaaggactgcagggactgccagtccccctgccccagggctcccggctatggggcact
gaggaccagccattgaggggtggaccctcagaaggcgtcacaagaacctggtcacaggactctgcctcct
cttcaactgaccagcctccatgctgcctccagaatggtctttctaatgtgtgaatcagagcacagcagcc
cctgcacaaagcccttccatgtcgcctctgcattcaggatcaaaccccgaccacctgcccaacctgctct
cctcttgccactgcctcttcctccctcattccaccttcccatgccctggatccatcaggccacttgatga
cccccaaccaagtggctcccacaccctgttttacaaaaaagaaaagaccagtccatgagggaggttttta
agggtttgtggaaaatgaaaattaggatttcatgatttttttttttcagtccccgtgaaggagagccctt
catttggagattatgttctttcggggagaggctgaggacttaaaatattcctgcatttgtgaaatgatgg
tgaaagtaagtggtagcttttcccttcttttttcttcttttttttgtgatgtcccaacttgtaaaaattaaa
agttatggtactatgttagccccataattttttttttcctttaaaacacttccataatctggactcctc
tgtccaggcactgctgcccagcctccaagctccatctccactccagatttttacagctgcctgcagtac
tttacctcctatcagaagtttctcagctcccaaggctctgagcaaatgtggctcctgggggttctttctt
cctctgctgaaggaataaattgctccttgacattgtagagcttctggcacttggagacttgtatgaaaga

tggctgtgcctctgcctgtctcccccaccgggctgggagctctgcagagcaggaaacatgactcgtatat
gtctcaggtccctgcagggccaagcacctagcctcgctcttggcaggtactcagcgaatgaatgctgtat
atgttgggtgcaaagttccctacttcctgtgacttcagctctgttttacaataaaatcttgaaaatgcct
aaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa.

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

MALETICRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIE
PHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFE
SAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE.

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

gggcagctccaccctgggagggactgtggcccaggtactgcccgggtgctactttatgggcagcagctca
gttgagttagagtctggaagacctcagaagacctcctgtcctatgaggccctccccatggctttaggggg
attataaaactaatcatcaaagccaagaaggcaagagcaagcatgtaccgctgaaaacacaagataactg
cataagtaatgactttcagtgcagattcatagctaacccataaactgctggggcaaaaatcatcttggaa
ggctctgaacctcagaaaggattcacaagacgatctgccgaccctctgggagaaaatccagcaag**ATG**ca
agccttcagaatctgggatgttaaccagaagaccttctatctgaggaacaaccaactagttgctggatac
ttgcaaggaccaaatgtcaatttagaagaaaagatagatgtggtacccattgagcctcatgctctgttct
tgggaatccatggagggaagatgtgcctgtcctgtgtcaagtctggtgatgagaccagactccagctgga
ggcagttaacatcactgacctgagcgagaacagaaagcaggacaagcgcttcgccttcatccgctcagac
agcggccccaccaccagttttgagtctgccgcctgccccggttggttcctctgcacagcgatggaagctg
accagcccgtcagcctcaccaatatgcctgacgaaggcgtcatggtcaccaaattctacttccaggagga
cgagtagtactgcccaggcctgcctgttcccattcttgcatggcaaggactgcagggactgccagtcccc
ctgccccagggctcccggctatgggggcactgaggaccagccattgaggggtggaccctcagaaggcgtc
acaagaacctggtcacaggactctgcctcctcttcaactgaccagcctccatgctgcctccagaatggtc
tttctaatgtgtgaatcagagcacagcagcccctgcacaaagcccttccatgtcgcctctgcattcagga
tcaaaccccgaccacctgcccaacctgctctcctcttgccactgcctcttcctccctcattccaccttcc
catgccctggatccatcaggccacttgatgacccccaaccaagtggctcccacaccctgttttacaaaaa
agaaaagaccagtccatgagggaggtttttaagggtttgtggaaaatgaaaattaggatttcatgatttt
ttttttcagtccccgtgaaggagagcccttcatttggagattatgttctttcggggagaggctgaggac
ttaaaatattcctgcatttgtgaaatgatggtgaaagtaagtggtagcttttcccttcttttttcttcttt
ttttgtgatgtcccaacttgtaaaaattaaaagttatggtactatgttagccccataatttttttttttcc
ttttaaaacacttccataatctggactcctctgtccaggcactgctgcccagcctccaagctccatctcc
actccagatttttacagctgcctgcagtactttacctcctatcagaagtttctcagctcccaaggctct
gagcaaatgtggctcctgggggttctttcttcctctgctgaaggaataaattgctccttgacattgtaga
gcttctggcacttggagacttgtatgaaagatggctgtgcctctgcctgtctcccccaccgggctgggag
ctctgcagagcaggaaacatgactcgtatatgtctcaggtccctgcagggccaagcacctagcctcgctc
ttggcaggtactcagcgaatgaatgctgtatatgttgggtgcaaagttccctacttcctgtgacttcagc
tctgttttacaataaaatcttgaaaatgcctaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa
aaaaaaaaaaaaa.

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

MQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCL
SCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEA
DQPVSLTNMPDEGVMVTKFYFQEDE.

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

agctccaccctgggagggactgtggcccaggtactgcccgggtgctactttatgggcagcagctcagttg
agttagagtctggaagacctcagaagacctcctgtcctatgaggccctcccc**ATG**gctttagagacgatc
tgccgaccctctgggagaaaatccagcaagatgcaagccttcagaatctgggatgttaaccagaagacct
tctatctgaggaacaaccaactagttgctggatacttgcaaggaccaaatgtcaatttagaagaaaagat
agatgtggtacccattgagcctcatgctctgttcttgggaatccatggagggaagatgtgcctgtcctgt
gtcaagtctggtgatgagaccagactccagctggaggcagttaacatcactgacctgagcgagaacagaa
agcaggacaagcgcttcgccttcatccgctcagacagtggccccaccaccagttttgagtctgccgcctg
ccccggttggttcctctgcacagcgatggaagctgaccagcccgtcagcctcaccaatatgcctgacgaa
ggcgtcatggtcaccaaattctacttccaggaggacgagtag.

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

MALETICRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIE
PHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFE
SAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE.

Human Recombinant IL-1Ra:

[112] 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.

[113] 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.

[114] 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).

[115] 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. This composition comprises one or more regions of SEQ ID NO: 15 or SEQ ID NO: 16. Furthermore, this composition comprises the entire sequence of either SEQ ID NO: 15 or SEQ ID NO: 16.

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

agctccaccctgggagggactgtggcccaggtactgcccgggtgctactttatgggcagcagctcagttg
agttagagtctggaagacctcagaagacctcctgtcctatgaggccctcccc**ATG**gctttagagacgatc
tgccgaccctctgggagaaaatccagcaagatgcaagccttcagaatctgggatgttaaccagaagacct
tctatctgaggaacaaccaactagttgctggatacttgcaaggaccaaatgtcaatttagaagaaaagat
agatgtggtacccattgagcctcatgctctgttcttgggaatccatggagggaagatgtgcctgtcctgt
gtcaagtctggtgatgagaccagactccagctggaggcagttaacatcactgacctgagcgagaacagaa
agcaggacaagcgcttcgccttcatccgctcagacagtggccccaccaccagttttgagtctgccgcctg
ccccggttggttcctctgcacagcgatggaagctgaccagcccgtcagcctcaccaatatgcctgacgaa
ggcgtcatggtcaccaaattctacttccaggaggacgagtag.

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

MRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALF
LGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACP
GWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE

IL-1 Receptors:

[118] 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.

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

tagacgcaccctctgaagatggtgactccctcctgagaagctggacccctttggtaaaagacaaggccttc
tccaagaagaat**ATG**aaagtgttactcagacttatttgtttcatagctctactgatttcttctctggagg
ctgataaatgcaaggaacgtgaagaaaaaataattttagtgtcatctgcaaatgaaattgatgttcgtcc
ctgtcctcttaacccaaatgaacacaaaggcactataacttggtataaagatgacagcaagacacctgta
tctacagaacaagcctccaggattcatcaacacaaagagaaactttggtttgttcctgctaaggtggagg
attcaggacattactattgcgtggtaagaaattcatcttactgcctcagaattaaaataagtgcaaaatt
tgtggagaatgagcctaacttatgttataatgcacaagccatatttaagcagaaactacccgttgcagga
gacggaggacttgtgtgcccttatatggagtttttaaaaatgaaaataatgagttacctaaattacagt
ggtataaggattgcaaacctctacttcttgacaatatacactttagtggagtcaaagataggctcatcgt
gatgaatgtggctgaaaagcatagagggaactatacttgtcatgcatcctacacatacttgggcaagcaa
tatcctattacccgggtaatagaatttattactctagaggaaaacaaacccacaaggcctgtgattgtga
gcccagctaatgagacaatggaagtagacttgggatcccagatacaattgatctgtaatgtcaccggcca
gttgagtgacattgcttactggaagtggaatgggtcagtaattgatgaagatgacccagtgctaggggaa
gactattacagtgtggaaaatcctgcaaacaaaagaaggagtaccctcatcacagtgcttaatatatcgg
aaattgaaagtagattttataaacatccatttacctgttttgccaagaatacacatggtatagatgcagc
atatatccagttaatatatccagtcactaatttccagaagcacatgattggtatatgtgtcacgttgaca
gtcataattgtgtgttctgttttcatctataaaatcttcaagattgacattgtgctttggtacagggatt
cctgctatgattttctcccaataaaagcttcagatggaaagacctatgacgcatatatactgtatccaaa
gactgttggggaagggtctacctctgactgtgatatttttgtgtttaaagtcttgcctgaggtcttggaa
aaacagtgtggatataagctgttcatttatggaagggatgactacgttggggaagacattgttgaggtca
ttaatgaaaacgtaaagaaaagcagaagactgattatcattttagtcagagaaacatcaggcttcagctg
gctgggtggttcatctgaagagcaaatagccatgtataatgctcttgttcaggatggaattaaagttgtc
ctgcttgagctggagaaaatccaagactatgagaaaatgccagaatcgattaaattcattaagcagaaac

atggggctatccgctggtcaggggactttacacagggaccacagtctgcaaagacaaggttctggaagaa
tgtcaggtaccacatgccagtccagcgacggtcaccttcatctaaacaccagttactgtcaccagccact
aaggagaaactgcaaagagaggctcacgtgcctctcgggtagcatggagaagttgccaagagttctttag
gtgcctcctgtcttatggcgttgcaggccaggttatgcctcatgctgacttgcagagttcatggaatgta
actatatcatcctttatccctgaggtcacctggaatcagattattaagggaataagccatgacgtcaata
gcagcccagggcacttcagagtagagggcttgggaagatcttttaaaaaggcagtaggcccggtgtggtg
gctcacgcctataatcccagcactttgggaggctgaagtgggtggatcaccagaggtcaggagttcgaga
ccagcccagccaacatggcaaaaccccatctctactaaaaatacaaaaatgagctaggcatggtggcaca
cgcctgtaatcccagctacacctgaggctgaggcaggagaattgcttgaaccggggagacggaggttgca
gtgagccgagtttgggccactgcactctagcctggcaacagagcaagactccgtctcaaaaaaagggcaa
taaatgccctctctgaatgtttgaactgccaagaaaaggcatggagacagcgaactagaagaaagggcaa
gaaggaaatagccaccgtctacagatggcttagttaagtcatccacagcccaagggcggggctatgcctt
gtctggggaccctgtagagtcactgaccctggagcggctctcctgagaggtgctgcaggcaaagtgagac
tgacacctcactgaggaagggagacatattcttggagaactttccatctgcttgtattttccatacacat
ccccagccagaagttagtgtccgaagaccgaattttattttacagagcttgaaaactcacttcaatgaac
aaagggattctccaggattccaaagttttgaagtcatcttagctttccacaggagggagagaacttaaaa
aagcaacagtagcagggaattgatccacttcttaatgctttcctccctggcatgaccatcctgtcctttg
ttattatcctgcattttacgtctttggaggaacagctccctagtggcttcctccgtctgcaatgtccctt
gcacagcccacacatgaaccatccttcccatgatgccgctcttctgtcatcccgctcctgctgaaacacc
tcccaggggctccacctgttcaggagctgaagcccatgctttcccaccagcatgtcactccagaccacc
tccctgccctgtcctccagcttcccctcgctgtcctgctgtgtgaattcccaggttggcctggtggccat
gtcgcctgcccccagcactcctctgtctctgctcttgcctcgacccttcctcctcctttgcctaggaggc
cttctcgcattttctctagctgatcagaattttaccaaaattcagaacatcctccaattccacagtctct
gggagactttccctaagaggcgacttcctctccagccttctctctctggtcaggcccactgcagagatgg
tggtgagcacatctgggaggctggtctccctccagctggaattgctgctctctgagggagaggctgtggt
ggctgtctctgtccctcactgccttccaggagcaatttgcacatgtaacatagatttatgtaatgcttta
tgtttaaaaacattccccaattatcttatttaatttttgcaattattctaattttatatatagagaaagt
gacctatttttaaaaaaatcacactctaagttctattgaacctaggacttgagcctccatttctggctt
ctagtctggtgttctgagtacttgatttcaggtcaataacggtccccccctcactccacactggcacgttt
gtgagaagaaatgacattttgctaggaagtgaccgagtctaggaatgcttttattcaagacaccaaattc
caaacttctaaatgttggaatttcaaaaattgtgtttagattttatgaaaaactcttctactttcatct
attctttccctagaggcaaacatttcttaaaatgtttcattttcattaaaaatgaaagccaaatttatat
gccaccgattgcaggacacaagcacagttttaagagttgtatgaacatggagaggacttttggtttttat
atttctcgtatttaatatgggtgaacaccaacttttatttggaataataatttttcctcctaaacaaaaac
acattgagtttaagtctctgactcttgcctttccacctgctttctcctgggcccgctttgcctgcttgaa
ggaacagtgctgttctggagctgctgttccaacagacagggcctagctttcatttgacacacagactaca
gccagaagcccatggagcagggatgtcacgtcttgaaaagcctattagatgttttacaaatttaattttg
cagattattttagtctgtcatccagaaaatgtgtcagcatgcatagtgctaagaaagcaagccaatttgg
aaacttaggttagtgacaaaattggccagagagtgggggtgatgatgaccaagaattacaagtagaatgg
cagctggaatttaaggagggacaagaatcaatggataagcgtgggtggaggaagatccaaacagaaaagt
gcaaagttattccccatcttccaagggttgaattctggaggaagaagacacattcctagttccccgtgaa
cttcctttgacttattgtccccactaaaacaaaacaaaaaacttttaatgccttccacattaattagatt
ttcttgcagtttttttatggcatttttttaaagatgccctaagtgttgaagaagagtttgcaaatgcaac
aaaatatttaattaccggttgttaaaactggtttagcacaatttatattttccctctcttgcctttctta
tttgcaataaaaggtattgagccatttttttaaatgacatttttgataaattatgtttgtactagttgatg
aaggagttttttttaacctgtttatataatttttgcagcagaagccaaatttttttgtatattaaagcacca
aattcatgtacagcatgcatcacggatcaatagactgtacttattttccaataaaattttcaaactttgt
actgttaaa.

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

MKVLLRLICFIALLISSLEADKCKEREEKIILVSSANEIDVRPCPLNPNEHKGTITWYKDDS
KTPVSTEQASRIHQHKEKLWFVPAKVEDSGHYYCVVRNSSYCLRIKISAKFVENEPNLC
YNAQAIFKQKLPVAGDGGLVCPYMEFFKNENNELPKLQWYKDCKPLLLDNIHFSGVKD

RLIVMNVAEKHRGNYTCHASYTYLGKQYPITRVIEFITLEENKPTRPVIVSPANETMEVD
LGSQIQLICNVTGQLSDIAYWKWNGSVIDEDDPVLGEDYYSVENPANKRRSTLITVLNIS
EIESRFYKHPFTCFAKNTHGIDAAYIQLIYPVTNFQKHMIGICVTLTVIIVCSVFIYKIFKIDI
VLWYRDSCYDFLPIKASDGKTYDAYILYPKTVGEGSTSDCDIFVFKVLPEVLEKQCGYK
LFIYGRDDYVGEDIVEVINENVKKSRRLIIILVRETSGFSWLGGSSEEQIAMYNALVQDGI
KVVLLELEKIQDYEKMPESIKFIKQKHGAIRWSGDFTQGPQSAKTRFWKNVRYHMPVQ
RRSPSSKHQLLSPATKEKLQREAHVPLG.

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

cccgtgaggaggaaaaggtgtgtccgctgccacccagtgtgagcgggtgacaccacccggttaggaaatc
ccagctcccaagagggtataaatccctgctttactgctgagctcctgctggaggtgaaagtctggcctgg
cagccttccccaggtgagcagcaacaaggccacgtgctgctgggtctcagtcctccacttcccgtgtcct
ctggaagttgtcaggagca**ATG**ttgcgcttgtacgtgttggtaatgggagtttctgccttcacccttcag
cctgcggcacacacaggggctgccagaagctgccggtttcgtgggaggcattacaagcgggagttcaggc
tggaaggggagcctgtagccctgaggtgcccccaggtgccctactggttgtgggcctctgtcagccccg
catcaacctgacatggcataaaaatgactctgctaggacggtcccaggagaagaagagacacggatgtgg
gcccaggacggtgctctgtggcttctgccagccttgcaggaggactctggcacctacgtctgcactacta
gaaatgcttcttactgtgacaaaatgtccattgagctcagagtttttgagaatacagatgctttcctgcc
gttcatctcatacccgcaaattttaaccttgtcaacctctggggtattagtatgccctgacctgagtgaa
ttcacccgtgacaaaactgacgtgaagattcaatggtacaaggattctcttcttttggataaagacaatg
agaaatttctaagtgtgaggggaccactcacttactcgtacacgatgtggccctggaagatgctggcta
ttaccgctgtgtcctgacatttgcccatgaaggccagcaatacaacatcactaggagtattgagctacgc
atcaagaaaaaaaaagaagagaccattcctgtgatcatttccccctcaagaccatatcagcttctctgg
ggtcaagactgacaatcccgtgtaaggtgtttctgggaaccggcacacccttaaccaccatgctgtggtg
gacggccaatgacacccacatagagagcgcctacccgggaggccgcgtgaccgaggggccacgccaggaa
tattcagaaaataatgagaactacattgaagtgccattgatttttgatcctgtcacaagagaggatttgc
acatggattttaaatgtgttgtccataataccctgagttttcagacactacgcaccacagtcaaggaagc
ctcctccacgttctcctggggcattgtgctggccccactttcactggccttcttggttttgggggaata
tggatgcacagacggtgcaaacacagaactggaaaagcagatggtctgactgtgctatggcctcatcatc
aagactttcaatcctatcccaagtgaaataaatggaatgaaataattcaaacacaaaaaaaaaaaaaaaa
aaaaaaaaaaaaa.

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

gggatgggagatactgttgtggtcacctctggaaaatacattctgctactcttaaaaactagtgacgctc
atacaaatcaacagaaagagcttctgaaggaagactttaaagctgcttctgccacgtgctgctgggtctc
agtcctccacttcccgtgtcctctggaagttgtcaggagca**ATG**ttgcgcttgtacgtgttggtaatggg
agtttctgccttcacccttcagcctgcggcacacacaggggctgccagaagctgccggtttcgtgggagg
cattacaagcgggagttcaggctggaaggggagcctgtagccctgaggtgcccccaggtgccctactggt
tgtgggcctctgtcagcccccgcatcaacctgacatggcataaaaatgactctgctaggacggtcccagg
agaagaagagacacggatgtgggcccaggacggtgctctgtggcttctgccagccttgcaggaggactct
ggcacctacgtctgcactactagaaatgcttcttactgtgacaaaatgtccattgagctcagagtttttg
agaatacagatgctttcctgccgttcatctcatacccgcaaattttaaccttgtcaacctctggggtatt
agtatgccctgacctgagtgaattcacccgtgacaaaactgacgtgaagattcaatggtacaaggattct
cttcttttggataaagacaatgagaaatttctaagtgtgaggggaccactcacttactcgtacacgatg
tggccctggaagatgctggctattaccgctgtgtcctgacatttgcccatgaaggccagcaatacaacat
cactaggagtattgagctacgcatcaagaaaaaaaaagaagagaccattcctgtgatcatttccccctc
aagaccatatcagcttctctggggtcaagactgacaatcccgtgtaaggtgtttctgggaaccggcacac
ccttaaccaccatgctgtggtggacggccaatgacacccacatagagagcgcctacccgggaggccgcgt
gaccgaggggccacgccaggaatattcagaaaataatgagaactacattgaagtgccattgatttttgat
cctgtcacaagagaggatttgcacatggattttaaatgtgttgtccataataccctgagttttcagacac
tacgcaccacagtcaaggaagcctcctccacgttctcctggggcattgtgctggccccactttcactggc

cttcttggttttgggggaatatggatgcacagacggtgcaaacacagaactggaaaagcagatggtctg
actgtgctatggcctcatcatcaagactttcaatcctatcccaagtgaaataaatggaatgaaataattc
aaacacaaaaaaaaaaaaaaaaaaaaaaaaaaa.

[123] 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):

MLRLYVLVMGVSAFTLQPAAHTGAARSCRFRGRHYKREFRLEGEPVALRCPQVPYWL
WASVSPRINLTWHKNDSARTVPGEEETRMWAQDGALWLLPALQEDSGTYVCTTRNAS
YCDKMSIELRVFENTDAFLPFISYPQILTLSTSGVLVCPDLSEFTRDKTDVKIQWYKDSLL
LDKDNEKFLSVRGTTHLLVHDVALEDAGYYRCVLTFAHEGQQYNITRSIELRIKKKKEE
TIPVIISPLKTISASLGSRLTIPCKVFLGTGTPLTTMLWWTANDTHIESAYPGGRVTEGPRQ
EYSENNENYIEVPLIFDPVTREDLHMDFKCVVHNTLSFQTLRTTVKEASSTFSWGIVLAP
LSLAFLVLGGIWMHRRCKHRTGKADGLTVLWPHHQDFQSYPK.

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

[124] 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.

[125] 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)

cagaagacctcctgtcctatgaggccctccccatggctttaggtaagctccttccactctcatttttca
cctgagaaatgagagaggaaaatgtctacaattggtgtttatcaaatgctttcaggctctggtgagcaag
cgtccaggaaaatgtcaagcgcatggagctccaggcctgtctgggggatctgggcacggggaggcatcca
tgggagaccatgcaggcactctgaggcaggggctgcaagctagtgcctgctggggcagcaggtgaacaga
gaggtgtaactgctgtgacagaagtcatggagtccttggagtgtgagggtcattttccactgttgataga
atagggaaattggtgaaatagccctgttaaatgagagaaagaacagtgtgagctcaatgagaaatactaa
tagaatgtggcactgagccacaaggtctgagggttgattgataaggaagggtggggactgtggagaatta
agggcttggcacaggtcagttccaccagttgtcacaagagaatgcaggctcaggtggccagaacttctcg
cttttccagaagagtccgatattctgatttcattatatatagtattctgattaaaccagacaataaagca
agcagataaaatatttaaagtataagctgccagtttgcaacctccggttaggatttgtgtggggcaaaga
aaaaaactctcaggatcattggtatgtagactctaattttaagtttctaatttaaaattggcccctgagg
ctgggcgtggtggctcacacctgtaatcccagcattttgggaggccaaggtgggtggatctcttgaggtc
aagagttcaaggcctgcctggccaacatggtgaaaccctgtctctattaaaaatacaaaaattagctggg
catggtggtgcatgtctgcaatcttagctacttgggtagctaaggcaggagaattgctggaacccgggag
gtagaggttgcagtgaatggagatcacaccactgcactccagtctgggcaatagagagagacgctctctc
taaaaaaaaatatgtaaagataaataaaatgaaataaaataggcctctaatgagcaggccattctccttt
ctgggtcttactttccttgcactcctttctgggtgttaagaggaggtctagaggaagctggacaactctt

agcttgtagtaagcacagtggaagtatcagctcttaatgggtcatggacacgttacgaagctaggcgccg
tgctgagcactttacatggtttatcccactgaaccctctcaataaccctatgaggaagggctattattgc
tcacattttcagaagaggaaatggatatagagagattagataatttgcccatggccagacagctagtata
agaggaggaggtggattgactgcagacattctgtcttcaaaccactacactatgctatggaggcacagag
acttaatgaaatcatggagaggggaattgctttgtcaaccacaagcagttattccgggggcagcagatcc
tcccctgtcccccagtggtacaatggtccctggtgggttgtgctacaatgttagcccatggtcttatgtg
tttttcaaatgtgtaaagtaggatgctggaaccactcttagaaccagataccaatacattgtgaagaaat
aaatctctgtgcttaaaactggttcatcccaaaatattttgaactgacacacaataggtgctaaataaat
gtgtgttaacttgaattggattgaattcgggaaaaaagtgcaataagcttagtgaagacaccatgttccc
tgggtagaggaaccacattctccatctaaggccaggagtatgggaggtatcaatgtttgcccagcacaga
acagggtgccaagaagagaaaagttgacggggtgcatactctgactggaaactggaagggtgagaacaga
gggtaaaggatagagatggaaccatgtgcatacactttgtgttaccttggacaagtcattcatttctctg
gacctctgctttctctctacacaatggggtcccaccacttcccttacagctgacttgtatgaagaaggag
gtggaggaggaggagaaggtgaagacaatg**CTG**actcaaagggtaaattatttttaggatccaagtttga
aaacaattttaggctactagatatgaacaacatcttgattatgtagttgaaggaaattaaagatgaatgg
tttaattaaaaattaatcagaatgaaaacgattgattactaatatatctgcaatggtttatttttcctgag
tggcagactcactaaggtttttgaatactcctgtgtgattgctctatgtatgtatgtatgtatgtatgta
tgcatgtatctatctatctgttgtctaatagaatggatcacatctctgctaataaaaacactacactggc
agggtacaattataatcattaactgtgcctggaatttgcagcagcagccaccagaggtaccagtgccctt
taagggttcataatttagaataatccaattatctgagtttttcagggactgaggggtttggcaaggtgta
gaactttcagtaataaagtcaagaaagtcctggacaaaccaaggtagttggtcactctagtccataacca
ggtaaagagctttccctgtaacctgtgtaaggttttagaatcatttctttccttattaccaaaaatcctc
cccaaattttcaagaaattatgaactaaatagttactctatgagataggagttcagcccaaaagaaacac
cataagaacaaatataattcttgcttatgttaaccatgcaatgaagcagagagaaaaagtcagtggcctc
tttaggaggactgtagtgtgggaagaaataactaaactgggtttcaatcctggcctggccaggatctgga
gcaagtgagttaatctttctaagccttgagtagtttataaaagaatggccactccatagacagagtagcc
tgaaccttgagttcttctataaagtcactatgaatttatactcattttgaaagtgggtgtcaatatgtct
gtccactttgcacagctgttatgtggacaaaaggagatctgtgtgaaagtgtaacacagagcctaaacta
taacaggtaagcaacacagttgtccct.

[126] 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):

[127] 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.

[128] IL-1RAP, transcript variant 1, is encoded by the following mRNA sequence (NCBI Accession No. NM_002182 and SEQ ID NO: 24):

tgccgggatccaggtctccggggtccgctttggccagaggcgcggaaggaagcagtgcccggcgacactg
cacccatcccggctgcttttgctgcgccctctcagcttcccaagaaaggcatcgtcatgtgatcatcacc
taagaactagaacatcagcaggccctagaagcctcactcttgcccctccctttaatatctcaaagg**ATG**a
cacttctgtggtgtgtagtgagtctctacttttatggaatcctgcaaagtgatgcctcagaacgctgcga
tgactggggactagacaccatgaggcaaatccaagtgtttgaagatgagccagctcgcatcaagtgccca
ctctttgaacacttcttgaaattcaactacagcacagcccattcagctggccttactctgatctggtatt
ggactaggcaggaccgggaccttgaggagccaattaacttccgcctccccgagaaccgcattagtaagga
gaaagatgtgctgtggttccggcccactctcctcaatgacactggcaactatacctgcatgttaaggaac
actacatattgcagcaaagttgcatttcccttggaagttgttcaaaaagacagctgtttcaattccccca
tgaaactcccagtgcataaactgtatatagaatatggcattcagaggatcacttgtccaaatgtagatgg
atattttccttccagtgtcaaaccgactatcacttggtatatgggctgttataaaatacagaattttaat
aatgtaatacccgaaggtatgaacttgagtttcctcattgccttaatttcaaataatggaaattacacat
gtgttgttacatatccagaaaatggacgtacgtttcatctcaccaggactctgactgtaaaggtagtagg
ctctccaaaaaatgcagtgccccctgtgatccattcacctaatgatcatgtggtctatgagaaagaacca
ggagaggagctactcattccctgtacggtctattttagttttctgatggattctcgcaatgaggtttggt
ggaccattgatggaaaaaaacctgatgacatcactattgatgtcaccattaacgaaagtataagtcatag
tagaacagaagatgaaacaagaactcagattttgagcatcaagaaagttacctctgaggatctcaagcgc
agctatgtctgtcatgctagaagtgccaaaggcgaagttccaaagcagccaaggtgaagcagaaagtgcc
agctccaagatacacagtggaactggcttgtggttttggagccacagtcctgctagtggtgattctcatt
gttgtttaccatgtttactggctagagatggtcctattttaccgggctcattttggaacagatgaaacca
ttttagatggaaaagagtatgatatttatgtatcctatgcaaggaatgcggaagaagaagaatttgtatt
actgaccctccgtggagttttggagaatgaatttggatacaagctgtgcatctttgaccgagacagtctg
cctgggggaattgtcacagatgagactttgagcttcattcagaaaagcagacgcctcctggttgttctaa
gccccaactacgtgctccagggaacccaagccctcctggagctcaaggctggcctagaaaatatggcctc
tcggggcaacatcaacgtcattttagtacagtacaaagctgtgaaggaaacgaaggtgaaagagctgaag
agggctaagacggtgctcacggtcattaaatggaaaggggaaaaatccaagtatccacagggcaggttct
ggaagcagctgcaggtggccatgccagtgaagaaaagtcccaggcggtctagcagtgatgagcagggcct
ctcgtattcatctttgaaaaatgtatgaaaggaataatgaaaagggtaaaaagaacaaggggtgctccag
gaagaaagagtccccccagtcttcattcgcagtttatggtttcataggcaaaaataatggtctaagcctc
ccaatagggataaatttagggtgactgtgtggctgactattctgcttcctcaggcaacactaaagtttag
aaagatatcatcaacgttctgtcaccagtctctgatgccactatgttctttgcaggcaaagacttgttca
atgcgaatttccccttctacattgtctatccctgtttttatatgtctccattctttttaaaatcttaaca
tatggagcagcctttcctatgaatttaaatatgcctttaaaataagtcactgttgacagggtcatgagtt
tccgagtatagttttctttttatcttatttttactcgtccgttgaaaagataatcaaggcctacatttta
gctgaggataatgaacttttttcctcattcggctgtataatacataaccacagcaagactgacatccact
taggatgatacaaagcagtgtaactgaaaatgtttctttttaattgatttaaaggacttgtcttctatacc
acccttgtcctcatctcaggtaatttatgaaatctatgtaaacttgaaaaatatttcttaatttttgtttt
ttgctccagtcaattcctgattatccacaggtcaacccacatttttttcattccttctccctatctgctta
tatcgcattgctcatttagagtttgcaggaggctccatactaggttcagtctgaaagaaatctcctaatg
gtgctatagagagggaggtaacagaaagactcttttagggcatttttctgactcatgaaaagagcacaga
aaaggatgtttggcaatttgtcttttaagtcttaaccttgctaatgtgaatactgggaaagtgatttttt
ctcactcgtttttgttgctccattgtaaagggcggaggtcagtcttagtggccttgagagttgcttttgg
cattaatattctaagagaattaactgtatttcctgtcacctattcactagtgcaggaaatatacttgctc
caaataagtcagtatgagaagtcactgtcaatgaaagttgttttgtttgttttcagtaatattttgctgt
ttttaagacttggaaaactaagtgcagagtttacagagtggtaaatatctatgttacatgtagattatac
atatatatacacacgtgtatatgagatatatatcttatatctccacaaacacaaattatatatatacata
tccacacacatacattacatatatctgtgtatataaatccacatgcacatgaaatatatatatatatata
atttgtgtgtgtgtatgtgtatgtatatgactttaaatagctatgggtacaatattaaaaaccactggaa
ctcttgtccagtttttaaattatgtttttactggaatgtttttgtgtcagtgttttctgtacatattatt
tgttaattcacagctcacagagtgatagttgtcatagttcttgccttccctaagtttatataaataactt
aagtattgctacagtttatctaggttgcagtggcatctgctgtgcacagagcttccatggtcactgctaa
gcagtagccagccatcgggcattaattgatttcctactatattcccagcagacacatttagaaactaagc
tatgttaacctcagtgctcaactatttgaactgttgagtgataaaggaaacaaatataactgtaaatgaa
tcttggtatcctgtgaaacagaataattcgtaatttaagaaagcccttatcccggtaacatgaatgttga
tgaacaaatgtaaaattatatcctatatttaagtacccataataaatcatttccctctataagtgttatt
gattattttaaattgaaaaaagtttcacttggatgaaaaaagtagaaaagtaggtcattcttggatctac
ttttttttagccttattaatatttttccctattagaaaccacaattactccctctattaacccttcactt

actagaccagaaaagaacttattccagataagctttgaatatcaattcttacataaactttaggcaaaca
gggaatagtctagtcaccaaaggaccattctcttgccaatgctgcattccttttgcacttttggattcca
tatttatcccaaatgctgttgggcacccctagaaataccttgatgtttttttctatttatatgcctgcctt
tggtacttaattttacaaatgctgtaatataaagcatatcaagtttatgtgatacgtatcattgcaagag
aatttgtttcaagatttttttttaatgttccagaagatggccaatagagaacattcaagggaaatgggga
aacataatttagagaacaagaacaaaccatgtctcaaatttttttaaaaaaaattaatggttttaaatat
atgctatagggacgttccatgcccaggttaacaaagaactgtgatatatagagtgtctaattacaaaatc
atatacgatttatttaattctcttctgtattgtaacttagatgattcccaaggactctaataaaaaatca
cttcattgtatttggaaacaaaaacatcattcattaattacttatttttctttccataggttttaatattt
tgagagtgtctttttttatttcattcatgaacttttgtatttttcatttttcatttgatttgtaaatttac
ttatgttaaaaataaaccatttatttttcagctttg.

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

MTLLWCVVSLYFYGILQSDASERCDDWGLDTMRQIQVFEDEPARIKCPLFEHFLKFNYS
TAHSAGLTLIWYWTRQDRDLEEPINFRLPENRISKEKDVLWFRPTLLNDTGNYTCMLRN
TTYCSKVAFPLEVVQKDSCFNSPMKLPVHKLYIEYGIQRITCPNVDGYFPSSVKPTITWY
MGCYKIQNFNNVIPEGMNLSFLIALISNNGNYTCVVTYPENGRTFHLTRTLTVKVVGSP
KNAVPPVIHSPNDHVVYEKEPGEELLIPCTVYFSFLMDSRNEVWWTIDGKKPDDITIDVT
INESISHSRTEDETRTQILSIKKVTSEDLKRSYVCHARSAKGEVAKAAKVKQKVPAPRYT
VELACGFGATVLLVVILIVVYHVYWLEMVLFYRAHFGTDETILDGKEYDIYVSYARNAE
EEEFVLLTLRGVLENEFGYKLCIFDRDSLPGGIVTDETLSFIQKSRRLLVVLSPNYVLQGT
QALLELKAGLENMASRGNINVILVQYKAVKETKVKELKRAKTVLTVIKWKGEKSKYPQ
GRFWKQLQVAMPVKKSPRRSSSDEQGLSYSSLKNV.

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

tgccgggatccaggtctccggggtccgctttggccagaggcgcggaaggaagcagtgcccggcgacactg
cacccatcccggctgcttttgctgcgccctctcagcttcccaagaaaggcatcgtcatgtgatcatcacc
taagaactagaacatcagcaggccctagaagcctcactcttgcccctccctttaatatctcaaagg**ATG**a
cacttctgtggtgtgtagtgagtctctacttttatggaatcctgcaaagtgatgcctcagaacgctgcga
tgactggggactagacaccatgaggcaaatccaagtgtttgaagatgagccagctcgcatcaagtgccca
ctctttgaacacttcttgaaattcaactacagcacagcccattcagctggccttactctgatctggtatt
ggactaggcaggaccgggaccttgaggagccaattaacttccgcctccccgagaaccgcattagtaagga
gaaagatgtgctgtggttccggcccactctcctcaatgacactggcaactatacctgcatgttaaggaac
actacatattgcagcaaagttgcatttcccttggaagttgttcaaaaagacagctgtttcaattccccca
tgaaactcccagtgcataaactgtatatagaatatggcattcagaggatcacttgtccaaatgtagatgg
atattttccttccagtgtcaaaccgactatcacttggtatatgggctgttataaaatacagaatttaat
aatgtaatacccgaaggtatgaacttgagtttcctcattgccttaatttcaaataatggaaattacacat
gtgttgttacatatccagaaaatggacgtacgtttcatctcaccaggactctgactgtaaaggtagtagg
ctctccaaaaaatgcagtgccccctgtgatccattcacctaatgatcatgtggtctatgagaaagaacca
ggagaggagctactcattccctgtacggtctattttagttttctgatggattctcgcaatgaggtttggt
ggaccattgatggaaaaaaacctgatgacatcactattgatgtcaccattaacgaaagtataagtcatag
tagaacagaagatgaaacaagaactcagattttgagcatcaagaaagttacctctgaggatctcaagcgc
agctatgtctgtcatgctagaagtgccaaaggcgaagttgccaaagcagccaaggtgaagcagaaaggta
atagatgcggtcagtgatgaatctctcagctccaaattaacattgtggtgaataaggacaaaaggagaga
ttgagaacaagagagctccagcacctagcccgacggcatctaacccatagtaatgaatcaaacttaaatg
aaaaatatgaaagttttcatctatgtaagatactcaaaatattgtttctgatattgttagtaccgtaatg
cccaaatgtagctaaaaaaatcgacgtgagtacagtgagacacaattttgtgtctgtacaattatgaaaa
attaaaaacaaagaaaatattcaaagctaccaaagatagaaaaaactggtagagccacatattgttggtg
aattattaagacccttttaaaaatcattcatggtagagtttaagagtcataaaaaagattgcatcatctg
acctaagactttcggaatttttcctgaacaaataacagaaagggaattatataccttttaatattattag
aagcattatctgtagttgtaaaacattattaatagcagccatccaattgtatgcaactaattaaggtatt

gaatgtttattttccaaaaatgcataattataatattattttaaacactatgtatcaatatttaagcagg
tttataatataccagcagccacaattgctaaaatgaaaatcatttaaattatgattttaaatggtataaa
catgatttctatgttgatagtactatattattctacaataaatggaaattataaagccttcttgtcagaa
gtgctgctcctaaaaaaaaaaaaaaaaaaaaa.

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

MTLLWCVVSLYFYGILQSDASERCDDWGLDTMRQIQVFEDEPARIKCPLFEHFLKFNYS
TAHSAGLTLIWYWTRQDRDLEEPINFRLPENRISKEKDVLWFRPTLLNDTGNYTCMLRN
TTYCSKVAFPLEVVQKDSCFNSPMKLPVHKLYIEYGIQRITCPNVDGYFPSSVKPTITWY
MGCYKIQNFNNVIPEGMNLSFLIALISNNGNYTCVVTYPENGRTFHLTRTLTVKVVGSP
KNAVPPVIHSPNDHVVYEKEPGEELLIPCTVYFSFLMDSRNEVWWTIDGKKPDDITIDVT
INESISHSRTEDETRTQILSIKKVTSEDLKRSYVCHARSAKGEVAKAAKVKQKGNRCGQ.

Interleukin-1 Receptor Associated Kinase 1 (IRAK1):

[132] 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.

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

cgcggacccggccggcccaggcccgcgcccgccgcggccctgagaggccccggcaggtcccggcccggcg
gcggcagcc**ATG**gccgggggccgggcccgggggagcccgcagcccccggcgcccagcacttcttgtacg
aggtgccgccctgggtcatgtgccgcttctacaaagtgatggacgccctggagcccgccgactggtgcca
gttcgccgccctgatcgtgcgcgaccagaccgagctgcggctgtgcgagcgctccgggcagcgcacggcc
agcgtcctgtggccctggatcaaccgcaacgcccgtgtggccgacctcgtgcacatcctcacgcacctgc
agctgctccgtgcgcgggacatcatcacagcctggcaccctcccgccccgcttccgtccccaggcaccac
tgccccgaggcccagcagcatccctgcacccgccgaggccgaggcctggagcccccggaagttgccatcc
tcagcctccaccttcctctccccagcttttccaggctcccagacccattcagggcctgagctcggcctgg
tcccaagccctgcttccctgtggcctccaccgccatctccagccccttcttctaccaagccaggcccaga
gagctcagtgtccctcctgcagggagcccgcccctttccgttttgctggcccctctgtgagatttcccgg
ggcacccacaacttctcggaggagctcaagatcggggagggtggctttgggtgcgtgtaccgggcggtga
tgaggaacacggtgtatgctgtgaagaggctgaaggagaacgctgacctggagtggactgcagtgaagca
gagcttcctgaccgaggtggagcagctgtccaggtttcgtcacccaaacattgtggactttgctggctac
tgtgctcagaacggcttctactgcctggtgtacggcttcctgcccaacggctccctggaggaccgtctcc
actgccagacccaggcctgcccacctctctcctggcctcagcgactggacatccttctgggtacagcccg
ggcaattcagtttctacatcaggacagccccagcctcatccatggagacatcaagagttccaacgtcctt
ctggatgagaggctgacacccaagctgggagactttggcctggcccggttcagccgctttgccgggtcca
gccccagccagagcagcatggtggcccggacacagacagtgcggggcaccctggcctacctgcccgagga
gtacatcaagacgggaaggctggctgtggacacggacaccttcagctttggggtggtagtgctagagacc

ttggctggtcagagggctgtgaagacgcacggtgccaggaccaagtatctgaaagacctggtggaagagg
aggctgaggaggctggagtggctttgagaagcacccagagcacactgcaagcaggtctggctgcagatgc
ctgggctgctcccatcgccatgcagatctacaagaagcacctggaccccaggcccgggccctgcccacct
gagctgggcctgggcctgggccagctggcctgctgctgcctgcaccgccgggccaaaaggaggcctccta
tgacccaggtgtacgagaggctagagaagctgcaggcagtggtggcgggggtgcccgggcattcggaggc
cgccagctgcatccccccttccccgcaggagaactcctacgtgtccagcactggcagagcccacagtggg
gctgctccatggcagcccctggcagcgccatcaggagccagtgcccaggcagcagagcagctgcagagag
gccccaaccagcccgtggagagtgacgagagcctaggcggcctctctgctgccctgcgctcctggcactt
gactccaagctgccctctggacccagcacccctcagggaggccggctgtcctcaggggacacggcagga
gaatcgagctgggggagtggcccaggatcccggcccacagccgtggaaggactggcccttggcagctctg
catcatcgtcgtcagagccaccgcagattatcatcaaccctgcccgacagaagatggtccagaagctggc
cctgtacgaggatggggccctggacagcctgcagctgctgtcgtccagctccctcccaggcttgggcctg
gaacaggacaggcaggggcccgaagaaagtgatgaatttcagagctgatgtgttcacctgggcagatccc
ccaaatccggaagtcaaagttctcatggtcagaagttctcatggtgcacgagtcctcagcactctgccgg
cagtgggggtgggggcccatgcccgcgggggagagaaggaggtggccctgctgttctaggctctgtgggc
ataggcaggcagagtggaaccctgcctccatgccagcatctgggggcaaggaaggctggcatcatccagt
gaggaggctggcgcatgttgggaggctgctggctgcacagacccgtgaggggaggagaggggctgctgtg
caggggtgtggagtagggagctggctcccctgagagccatgcagggcgtctgcagcccaggcctctggca
gcagctctttgcccatctctttggacagtggccaccctgcacaatggggccgacgaggcctagggccctc
ctacctgcttacaatttggaaaagtgtggccgggtgcggtggctcacgcctgtaatcccagcactttggg
aggccaaggcaggaggatcgctggagcccagtaggtcaagaccagccagggcaacatgatgagaccctgt
ctctgccaaaaaatttttaaactattagcctggcgtggtagcgcacgcctgtggtcccagctgctgggg
aggctgaagtaggaggatcatttatgcttgggaggtcgaggctgcagtgagtcatgattgtatgactgca
ctccagcctgggtgacagagcaagaccctgtttcaaaaagaaaaaccctgggaaaagtgaagtatggctg
taagtctcatggttcagtcctagcaagaagcgagaattctgagatcctccagaaagtcgagcagcaccca
cctccaacctcgggccagtgtcttcaggctttactggggacctgcgagctggcctaatgtggtggcctgc
aagccaggccatccctgggcgccacagacgagctccgagccaggtcaggcttcggaggccacaagctcag
cctcaggcccaggcactgattgtggcagaggggccactacccaaggtctagctaggcccaagacctagtt
acccagacagtgagaagcccctggaaggcagaaaagttgggagcatggcagacagggaagggaaacattt
tcagggaaaagacatgtatcacatgtcttcagaagcaagtcaggtttcatgtaaccgagtgtcctcttgc
gtgtccaaaagtagcccagggctgtagcacaggcttcacagtgattttgtgttcagccgtgagtcacact
acatgcccccgtgaagctgggcattggtgacgtccaggttgtccttgagtaataaaaacgtatgttgcaa
taaaaaaaaaaaaaaaaaa.

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

MAGGPGPGEPAAPGAQHFLYEVPPWVMCRFYKVMDALEPADWCQFAALIVRDQTELR
LCERSGQRTASVLWPWINRNARVADLVHILTHLQLLRARDIITAWHPPAPLPSPGTTAPR
PSSIPAPAEAEAWSPRKLPSSASTFLSPAFPGSQTHSGPELGLVPSPASLWPPPPSPAPSST
KPGPESSVSLLQGARPFPFCWPLCEISRGTHNFSEELKIGEGGFGCVYRAVMRNTVYAV
KRLKENADLEWTAVKQSFLTEVEQLSRFRHPNIVDFAGYCAQNGFYCLVYGFLPNGSL
EDRLHCQTQACPPLSWPQRLDILLGTARAIQFLHQDSPSLIHGDIKSSNVLLDERLTPKLG
DFGLARFSRFAGSSPSQSSMVARTQTVRGTLAYLPEEYIKTGRLAVDTDTFSFGVVVLET
LAGQRAVKTHGARTKYLKDLVEEEAEEAGVALRSTQSTLQAGLAADAWAAPIAMQIY
KKHLDPRPGPCPPELGLGLGQLACCCLHRRAKRRPPMTQVYERLEKLQAVVAGVPGHS
EAASCIPPSPQENSYVSSTGRAHSGAAPWQPLAAPSGASAQAAEQLQRGPNQPVESDES
LGGLSAALRSWHLTPSCPLDPAPLREAGCPQGDTAGESSWGSGPGSRPTAVEGLALGSS
ASSSSEPPQIIINPARQKMVQKLALYEDGALDSLQLLSSSSLPGLGLEQDRQGPEESDEFQ
S.

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

cgcggacccggccggcccaggcccgcgcccgccgcggccctgagaggccccggcaggtcccggcccggcg
gcggcagcc**ATG**gccgggggccgggcccgggggagcccgcagcccccggcgcccagcacttcttgtacg
aggtgccgccctgggtcatgtgccgcttctacaaagtgatggacgccctggagcccgccgactggtgcca
gttcgccgccctgatcgtgcgcgaccagaccgagctgcggctgtgcgagcgctccgggcagcgcacggcc
agcgtcctgtggccctggatcaaccgcaacgcccgtgtggccgacctcgtgcacatcctcacgcacctgc
agctgctccgtgcgcgggacatcatcacagcctggcaccctcccgccccgcttccgtccccaggcaccac
tgccccgaggcccagcagcatccctgcacccgccgaggccgaggcctggagcccccggaagttgccatcc
tcagcctccaccttcctctccccagcttttccaggctcccagacccattcagggcctgagctcggcctgg
tcccaagccctgcttccctgtggcctccaccgccatctccagccccttcttctaccaagccaggcccaga
gagctcagtgtccctcctgcagggagcccgccccttttccgttttgctggcccctctgtgagatttcccgg
ggcacccacaacttctcggaggagctcaagatcggggagggtggctttgggtgcgtgtaccgggcggtga
tgaggaacacggtgtatgctgtgaagaggctgaaggagaacgctgacctggagtggactgcagtgaagca
gagcttcctgaccgaggtggagcagctgtccaggtttcgtcacccaaacattgtggactttgctggctac
tgtgctcagaacggcttctactgcctggtgtacggcttcctgcccaacggctccctggaggaccgtctcc
actgccagacccaggcctgcccacctctctcctggcctcagcgactggacatccttctgggtacagcccg
ggcaattcagtttctacatcaggacagccccagcctcatccatggagacatcaagagttccaacgtcctt
ctggatgagaggctgacacccaagctgggagactttggcctggcccggttcagccgctttgccgggtcca
gccccagccagagcagcatggtggcccggacacagacagtgcggggcaccctggcctacctgcccgagga
gtacatcaagacgggaaggctggctgtggacacggacaccttcagctttggggtggtagtgctagagacc
ttggctggtcagagggctgtgaagacgcacggtgccaggaccaagtatctgaaagacctggtggaagagg
aggctgaggaggctggagtggctttgagaagcacccagagcacactgcaagcaggtctggctgcagatgc
ctgggctgctcccatcgccatgcagatctacaagaagcacctggaccccaggcccgggccctgcccacct
gagctgggcctgggcctgggccagctggcctgctgctgcctgcaccgccgggccaaaaggaggcctccta
tgacccaggagaactcctacgtgtccagcactggcagagcccacagtggggctgctccatggcagcccct
ggcagcgccatcaggagccagtgcccaggcagcagagcagctgcagagaggccccaaccagcccgtggag
agtgacgagagcctaggcggcctctctgctgccctgcgctcctggcacttgactccaagctgccctctgg
acccagcacccctcagggaggccggctgtcctcagggggacacggcaggagaatcgagctgggggagtgg
cccaggatcccggcccacagccgtggaaggactggcccttggcagctctgcatcatcgtcgtcagagcca
ccgcagattatcatcaaccctgcccgacagaagatggtccagaagctggccctgtacgaggatggggccc
tggacagcctgcagctgctgtcgtccagctccctcccaggcttgggcctggaacaggacaggcaggggcc
cgaagaaagtgatgaatttcagagctgatgtgttcacctgggcagatcccccaaatccggaagtcaaagt
tctcatggtcagaagttctcatggtgcacgagtcctcagcactctgccggcagtgggggtgggggcccat
gcccgcgggggagagaaggaggtggccctgctgttctaggctctgtgggcataggcaggcagagtggaac
cctgcctccatgccagcatctgggggcaaggaaggctggcatcatccagtgaggaggctggcgcatgttg
ggaggctgctggctgcacagacccgtgaggggaggagaggggctgctgtgcaggggtgtggagtagggag
ctggctcccctgagagccatgcagggcgtctgcagcccaggcctctggcagcagctctttgcccatctct
ttggacagtggccaccctgcacaatggggccgacgaggcctagggccctcctacctgcttacaatttgga
aaagtgtggccgggtgcggtggctcacgcctgtaatcccagcactttgggaggccaaggcaggaggatcg
ctggagcccagtaggtcaagaccagccagggcaacatgatgagaccctgtctctgccaaaaaattttttta
aactattagcctggcgtggtagcgcacgcctgtggtcccagctgctggggaggctgaagtaggaggatca
tttatgcttgggaggtcgaggctgcagtgagtcatgattgtatgactgcactccagcctgggtgacagag
caagaccctgtttcaaaaagaaaaaccctgggaaaagtgaagtatggctgtaagtctcatggttcagtcc
tagcaagaagcgagaattctgagatcctccagaaagtcgagcagcacccacctccaacctcgggccagtg
tcttcaggctttactggggacctgcgagctggcctaatgtggtggcctgcaagccaggccatccctgggc
gccacagacgagctccgagccaggtcaggcttcggaggccacaagctcagcctcaggcccaggcactgat
tgtggcagaggggccactacccaaggtctagctaggcccaagacctagttacccagacagtgagaagccc
ctggaaggcagaaaagttgggagcatggcagacagggaagggaaacattttcagggaaaagacatgtatc
acatgtcttcagaagcaagtcaggtttcatgtaaccgagtgtcctcttgcgtgtccaaaagtagcccagg
gctgtagcacaggcttcacagtgattttgtgttcagccgtgagtcacactacatgcccccgtgaagctgg
gcattggtgacgtccaggttgtccttgagtaataaaaacgtatgttgcaataaaaaaaaaaaaaaaaaa.

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

MAGGPGPGEPAAPGAQHFLYEVPPWVMCRFYKVMDALEPADWCQFAALIVRDQTELR
LCERSGQRTASVLWPWINRNARVADLVHILTHLQLLRARDIITAWHPPAPLPSPGTTAPR
PSSIPAPAEAEAWSPRKLPSSASTFLSPAFPGSQTHSGPELGLVPSPASLWPPPPSPAPSST
KPGPESSVSLLQGARPFPFCWPLCEISRGTHNFSEELKIGEGGFGCVYRAVMRNTVYAV
KRLKENADLEWTAVKQSFLTEVEQLSRFRHPNIVDFAGYCAQNGFYCLVYGFLPNGSL
EDRLHCQTQACPPLSWPQRLDILLGTARAIQFLHQDSPSLIHGDIKSSNVLLDERLTPKLG
DFGLARFSRFAGSSPSQSSMVARTQTVRGTLAYLPEEYIKTGRLAVDTDTFSFGVVVLET
LAGQRAVKTHGARTKYLKDLVEEEAEEAGVALRSTQSTLQAGLAADAWAAPIAMQIY
KKHLDPRPGPCPPELGLGLGQLACCCLHRRAKRRPPMTQENSYVSSTGRAHSGAAPWQ
PLAAPSGASAQAAEQLQRGPNQPVESDESLGGLSAALRSWHLTPSCPLDPAPLREAGCP
QGDTAGESSWGSGPGSRPTAVEGLALGSSASSSSEPPQIIINPARQKMVQKLALYEDGAL
DSLQLLSSSSLPGLGLEQDRQGPEESDEFQS.

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

cgcggacccggccggcccaggcccgcgcccgccgcggccctgagaggccccggcaggtcccggccccggcg
gcggcagcc**ATG**gccgggggccgggcccgggggagcccgcagcccccggcgcccagcacttcttgtacg
aggtgccgccctgggtcatgtgccgcttctacaaagtgatggacgccctggagcccgccgactggtgcca
gttcgccgccctgatcgtgcgcgaccagaccgagctgcggctgtgcgagcgctccgggcagcgcacggcc
agcgtcctgtggccctggatcaaccgcaacgcccgtgtggccgacctcgtgcacatcctcacgcacctgc
agctgctccgtgcgcgggacatcatcacagcctggcaccctcccgccccgcttccgtccccaggcaccac
tgccccgaggcccagcagcatccctgcacccgccgaggccgaggcctggagcccccggaagttgccatcc
tcagcctccaccttcctctccccagcttttccaggctcccagacccattcagggcctgagctcggcctgg
tcccaagccctgcttccctgtggcctccaccgccatctccagccccttcttctaccaagccaggcccaga
gagctcagtgtccctcctgcagggagcccgccccttttccgttttgctggcccctctgtgagatttcccgg
ggcacccacaacttctcggaggagctcaagatcggggagggtggctttgggtgcgtgtaccgggcggtga
tgaggaacacggtgtatgctgtgaagaggctgaaggagaacgctgacctggagtggactgcagtgaagca
gagcttcctgaccgaggtggagcagctgtccaggtttcgtcacccaaacattgtggactttgctggctac
tgtgctcagaacggcttctactgcctggtgtacggcttcctgcccaacggctccctggaggaccgtctcc
actgccagacccaggcctgcccacctctctcctggcctcagcgactggacatccttctgggtacagcccg
ggcaattcagtttctacatcaggacagccccagcctcatccatggagacatcaagagttccaacgtcctt
ctggatgagaggctgacacccaagctgggagactttggcctggcccggttcagccgctttgccgggtcca
gccccagccagagcagcatggtggcccggacacagacagtgcggggcaccctggcctacctgcccgagga
gtacatcaagacgggaaggctggctgtggacacggacaccttcagctttggggtggtagtgctagagacc
ttggctggtcagagggctgtgaagacgcacggtgccaggaccaagtatctggtgtacgagaggctagaga
agctgcaggcagtggtggcgggggtgcccgggcattcggaggccgccagctgcatccccccttccccgca
ggagaactcctacgtgtccagcactggcagagcccacagtggggctgctccatggcagcccctggcagcg
ccatcaggagccagtgcccaggcagcagagcagctgcagagaggccccaaccagcccgtggagagtgacg
agagcctaggcggcctctctgctgccctgcgctcctggcacttgactccaagctgccctctggacccagc
acccctcagggaggccggctgtcctcaggggacacggcaggagaatcgagctgggggagtggcccagga
tcccggcccacagccgtggaaggactggcccttggcagctctgcatcatcgtcgtcagagccaccgcaga
ttatcatcaaccctgcccgacagaagatggtccagaagctggccctgtacgaggatggggccctggacag
cctgcagctgctgtcgtccagctccctcccaggcttgggcctggaacaggacaggcaggggcccgaagaa
agtgatgaatttcagagctgatgtgttcacctgggcagatccccaaatccggaagtcaaagttctcatg
gtcagaagttctcatggtgcacgagtcctcagcactctgccggcagtgggggtgggggcccatgcccgcg
ggggagagaaggaggtggccctgctgttctaggctctgtgggcataggcaggcagagtggaaccctgcct
ccatgccagcatctgggggcaaggaaggctggcatcatccagtgaggaggctggcgcatgttgggaggct
gctggctgcacagacccgtgaggggaggagaggggctgctgtgcaggggtgtggagtagggagctggctc
ccctgagagccatgcagggcgtctgcagcccaggcctctggcagcagctctttgcccatctctttggaca
gtggccaccctgcacaatggggccgacgaggcctagggccctcctacctgcttacaatttggaaaagtgt
ggccgggtgcggtggctcacgcctgtaatcccagcactttgggaggccaaggcaggaggatcgctggagc
ccagtaggtcaagaccagccagggcaacatgatgagaccctgtctctgccaaaaaatttttttaaactatt
agcctggcgtggtagcgcacgcctgtggtcccagctgctggggaggctgaagtaggaggatcatttatgc
ttgggaggtcgaggctgcagtgagtcatgattgtatgactgcactccagcctgggtgacagagcaagacc

ctgtttcaaaaagaaaaaccctgggaaaagtgaagtatggctgtaagtctcatggttcagtcctagcaag
aagcgagaattctgagatcctccagaaagtcgagcagcacccacctccaacctcgggccagtgtcttcag
gctttactggggacctgcgagctggcctaatgtggtggcctgcaagccaggccatccctgggcgccacag
acgagctccgagccaggtcaggcttcggaggccacaagctcagcctcaggcccaggcactgattgtggca
gaggggccactacccaaggtctagctaggcccaagacctagttacccagacagtgagaagcccctggaag
gcagaaaagttgggagcatggcagacagggaagggaaacattttcagggaaaagacatgtatcacatgtc
ttcagaagcaagtcaggtttcatgtaaccgagtgtcctcttgcgtgtccaaaagtagcccagggctgtag
cacaggcttcacagtgattttgtgttcagccgtgagtcacactacatgcccccgtgaagctgggcattgg
tgacgtccaggttgtccttgagtaataaaaacgtatgttgcaataaaaaaaaaaaaaaaaaa.

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

MAGGPGPGEPAAPGAQHFLYEVPPWVMCRFYKVMDALEPADWCQFAALIVRDQTELR
LCERSGQRTASVLWPWINRNARVADLVHILTHLQLLRARDIITAWHPPAPLPSPGTTAPR
PSSIPAPAEAEAWSPRKLPSSASTFLSPAFPGSQTHSGPELGLVPSPASLWPPPPSPAPSST
KPGPESSVSLLQGARPFPFCWPLCEISRGTHNFSEELKIGEGGFGCVYRAVMRNTVYAV
KRLKENADLEWTAVKQSFLTEVEQLSRFRHPNIVDFAGYCAQNGFYCLVYGFLPNGSL
EDRLHCQTQACPPLSWPQRLDILLGTARAIQFLHQDSPSLIHGDIKSSNVLLDERLTPKLG
DFGLARFSRFAGSSPSQSSMVARTQTVRGTLAYLPEEYIKTGRLAVDTDTFSFGVVVLET
LAGQRAVKTHGARTKYLVYERLEKLQAVVAGVPGHSEAASCIPPSPQENSYVSSTGRA
HSGAAPWQPLAAPSGASAQAAEQLQRGPNQPVESDESLGGLSAALRSWHLTPSCPLDP
APLREAGCPQGDTAGESSWGSGPGSRPTAVEGLALGSSASSSSEPPQIIINPARQKMVQK
LALYEDGALDSLQLLSSSSLPGLGLEQDRQGPEESDEFQS.

Silencing Expression with MicroRNAs

[139] 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 an 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

[140] As used herein, the term "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.

[141] 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.

[142] The inhibition of an activity of an inflammatory interleukin-1 cytokine is determined by sampling an ocular or adnexal tissue or fluid 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.

[143] Specifically, Figure 4 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.

[144] 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.

[145] 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 in an ocular or adnexal tissue or fluid is indicative of inhibition of an inflammatory 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 inflammatory interleukin-1 cytokine.

Pharmaceutically-Appropriate Carriers

[146] Exemplary compounds incorporated to facilitate and expedite transdermal 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.

[147] 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, carboxymethylcellulose (CMC), hyaluronic acid, cyclodextrin, and petroleum.

Drug Delivery by Contact Lens

[148] The invention comprises a contact lens and a composition that inhibits an activity of an inflammatory interleukin-1 cytokine. For example, the composition is incorporated into or coated onto said lens. The composition is chemically bound or physically entrapped by the

contact lens polymer. Alternatively, a color additive is chemically bound or physically entrapped by the polymer composition that is released at the same rate as the therapeutic drug composition, such that changes in the intensity of the color additive indicate changes in the amount or dose of therapeutic drug composition remaining bound or entrapped within the polymer. Alternatively, or in addition, an ultraviolet (UV) absorber is chemically bound or physically entrapped within the contact lens polymer. The contact lens is either hydrophobic or hydrophilic.

[149] Exemplary materials used to fabricate a hydrophobic lens with means to deliver the compositions of the present invention include, but are not limited to, amefocon A, amsilfocon A, aquilafocon A, arfocon A, cabufocon A, cabufocon B, carbosilfocon A, crilfocon A, crilfocon B, dimefocon A, enflufocon A, enflofocon B, erifocon A, flurofocon A, flusilfocon A, flusilfocon B, flusilfocon C, flusilfocon D, flusilfocon E, hexafocon A, hofocon A, hybufocon A, itabisfluorofocon A, itafluorofocon A, itafocon A, itafocon B, kolfocon A, kolfocon B, kolfocon C, kolfocon D, lotifocon A, lotifocon B, lotifocon C, melafocon A, migafocon A, nefocon A, nefocon B, nefocon C, onsifocon A, oprifocon A, oxyfluflocon A, paflufocon B, paflufocon C, paflufocon D, paflufocon E, paflufocon F, pasifocon A, pasifocon B, pasifocon C, pasifocon D, pasifocon E, pemufocon A, porofocon A, porofocon B, roflufocon A, roflufocon B, roflufocon C, roflufocon D, roflufocon E, rosilfocon A, satafocon A, siflufocon A, silafocon A, sterafocon A, sulfocon A, sulfocon B, telafocon A, tisilfocon A, tolofocon A, trifocon A, unifocon A, vinafocon A, and wilofocon A.

[150] Exemplary materials used to fabricate a hydrophilic lens with means to deliver the compositions of the present invention include, but are not limited to, abafilcon A, acofilcon A, acofilcon B, acquafilcon A, alofilcon A, alphafilcon A, amfilcon A, astifilcon A, atlafilcon A, balafilcon A, bisfilcon A, bufilcon A, comfilcon A, crofilcon A, cyclofilcon A, darfilcon A, deltafilcon A, deltafilcon B, dimefilcon A, droxfilcon A, elastofilcon A, epsilfilcon A, esterifilcon A, etafilcon A, focofilcon A, galyfilcon A, genfilcon A, govafilcon A, hefilcon A, hefilcon B, hefilcon C, hilafilcon A, hilafilcon B, hioxifilcon A, hioxifilcon B, hioxifilcon C, hydrofilcon A, lenefilcon A, licryfilcon A, licryfilcon B, lidofilcon A, lidofilcon B, lotrafilcon A, lotrafilcon B, mafilcon A, mesafilcon A, methafilcon B, mipafilcon A, nelfilcon A, netrafilcon A, ocufilcon A, ocufilcon B, C, ocufilcon D, ocufilcon E, ofilcon A, omafilcon A, oxyfilcon A, pentafilcon A, perfilcon A, pevafilcon A, phemfilcon A, polymacon, senofilcon A, silafilcon A, siloxyfilcon A, surfilcon A, tefilcon A, tetrafilcon A, trilfilcon A, vifilcon A, vifilcon B, and xylofilcon A.

EXAMPLES

EXAMPLE 1: The Ocular Surface Disease Index (OSDI)

[151] The Ocular Surface Disease Index (OSDI) is a 12-item questionnaire that provides a rapid assessment of the symptoms of ocular irritation consistent with ocular surface disease, including posterior blepharitis and dry eye disease, and their impact on vision-related functioning (Figure 1). The 12 items of the OSDI questionnaire are graded on a scale of 0 to 4, where 0 indicates none of the time; 1, some of the time; 2, half of the time; 3, most of the time; and 4, all of the time. The total OSDI score is then calculated on the basis of the following formula: OSDI=[(sum of scores for all questions answered) x 100]/[(total number of questions answered) x 4]. Thus, the OSDI is scored on a scale of 0 to 100, with higher scores representing greater disability. A negative change from baseline indicates an improvement in vision-related function and the ocular inflammatory disorders described herein. For the therapeutic method described herein, treatment is considered more effective than control (vehicle) as indicated by a mean change (decrease) from baseline for the OSDI of >10 units compared to control.

[152] Therapeutic treatment is considered more effective than the vehicle as indicated by a mean change from baseline of average score (0 -100) for the Ocular Surface Disease Index (OSDI) of >10 units better than vehicle.

EXAMPLE 2: Tear Film Break-up Time

[153] The standard TBUT measurement is performed by moistening a fluorescein strip with sterile non-preserved saline and applying it to the inferior tarsal conjunctiva. After several blinks, the tear film is examined using a broad beam of the slit lamp with a blue filter. The time lapse between the last blink and the appearance of the first randomly distributed dark discontinuity in the fluorescein stained tear film is measured three times and the mean value of the measurements is calculated. The tear break-up time is evaluated prior to the instillation of any eye drops and before the eyelids are manipulated in any way. Break-up times less than 10 seconds are considered abnormal. A positive change from baseline indicates improvement in symptoms of the ocular inflammatory disorders described herein. The treatment described herein, leads to an improvement in TBUT significantly greater than that observed from treatment with vehicle alone.

EXAMPLE 3: Corneal and Conjunctival Staining

[154] Corneal staining is a measure of epithelial disease, or break in the epithelial barrier of the ocular surface, typically seen with ocular surface disorders such as posterior blepharitis and dry eye, among others. Importantly, corneal staining can exist even without clinically evident dry eye, if there is significant lid disease, such as posterior blepharitis. Corneal staining is highly correlated with ocular discomfort in many, though not all patients; in general corneal staining is associated with high scores in the OSDI, as described above. For corneal fluorescein staining, saline-moistened fluorescein strips or 1% sodium fluorescein solution are used to stain the tear film. The entire cornea is then examined using slit-lamp evaluation with a yellow barrier filter (#12 Wratten) and cobalt blue illumination (staining is more intense when it is observed with a yellow filter). Staining is graded according to the Oxford Schema (Figure 2).

[155] Conjunctival staining is a measure of epithelial disease or break in the epithelial barrier of the ocular surface, typically seen with ocular surface disorders such as posterior blepharitis and dry eye, among others. Importantly, conjunctival staining, similar to corneal staining, can exist even without clinically evident dry eye, if there is significant lid disease, such as posterior blepharitis. Conjunctival staining can also correlate with symptoms of ocular irritation and high OSDI scores as described above. Conjunctival staining is performed under the slit-lamp using lissamine green. Saline-moistened strip or 1% lissamine green solution is used to stain the tear film, and interpalpebral conjunctival staining is evaluated more than 30 seconds, but less than 2 minutes, later. Using white light of moderate intensity, only the interpalpebral region of the nasal and temporal conjunctival staining is graded using the Oxford Schema (above). The treatment described herein leads to decreases in ocular staining scores beyond what is observed with the vehicle alone.

[156] Therapeutic treatment is considered more effective than vehicle as indicated by a mean change from baseline in average score (0-5 scale) for corneal and conjunctival staining of > 1 unit better than vehicle, e.g. as detected using the Oxford Schema.

EXAMPLE 4: Schirmer Test

[157] The Schirmer test is performed in the presence and in the absence of anesthesia by placing a narrow filter-paper strip (5 x 3 5mm strip of Whatman #41 filter paper) in the inferior cul-de-sac. This test is conducted in a dimly lit room. The patient gently closes his/her eyes until five minutes have elapsed and the strips are removed. Because the tear front will continue advancing a few millimeters after it has been removed from the eyes, the tear front is marked with a ball-point pen at precisely five minutes. Aqueous tear production is measured by the

length in millimeters that the strip wets during 5 minutes. Results of 10 mm or less for the Schirmer test without anesthesia and 5 mm or less for the Schirmer test with anesthesia are considered abnormal. A positive change from baseline indicates improvement of one or more symptoms of an ocular inflammatory disorder described herein.

EXAMPLE 5: Meibomian Gland Evaluation

[158] In the center of the lower lid, 10 adjacent central glands are located on both sides and the glands are expressed by applying a firm digital pressure at the base of the glands. The number of glands expressed for each eye is documented. The quality of secretion is described as follows:

- Clear excreta or clear with small particles (0)
- Opaque excreta with normal viscosity (1)
- Opaque excreta with increased viscosity (2)
- Secretions retain shape after expression (3)

[159] Posterior blepharitis is associated with lid inflammation and alterations in the quantity and/or quality of the meibomian gland secretions, with severe disease associated with quality grades 2-3, as described above. The treatment described herein leads to improvement in meibomian secretion characterized by a decrease in this score; for example, from 3 to 2, or from 2 to 1. An improvement is indicated by a mean change from baseline (0-3 scale) for meibomian gland secretion quality of > 1 unit better than vehicle.

EXAMPLE 6: Lid and Lid Margin Erythema

[160] Lid margin vascular injection (erythema) is defined as a red discoloration, compared to the surrounding eyelid skin and is graded as follows:

None	(0):	none
Mild	(1):	redness localized to a small region of the lid margin(s) or skin
Moderate	(2):	redness of most of the lid margin(s)
Severe	(3):	redness of most or all the lid margin(s) and skin
Very Severe	(4):	marked diffuse redness of both lid margins and skin

The presence or absence of tarsal telangiectasis is also noted. Lid telangiectasia is defined as the presence of at least two blood vessels along the eyelid margin.

EXAMPLE 7: Conjunctiva Hyperemia

[161] Bulbar conjunctival hyperemia is graded as follows:

None	(0):	none
Mild	(1):	slight localized injection
Moderate	(2):	pink color, confined to palpebral or bulbar conjunctiva
Severe	(3):	red color of the palpebral and/or bulbar conjunctiva

Very Severe (4): marked dark redness of the palpebral and/or bulbar conjunctiva

The presence or absence of tarsal papillary hypertrophy is also noted.

EXAMPLE 8: Topical Administration of IL-1Ra for Treating Posterior Blepharitis

[162] The following study evaluates the therapeutic benefit of topically administering a solution comprising a known, and commercially-available, recombinant IL-1 receptor antagonist, Anakinra (Kineret®), versus vehicle to subjects with inflammatory conditions affecting one or more ocular and/or adnexal tissues.

[163] The following is a prospective, single-center, randomized, double-masked, vehicle-controlled, parallel-group clinical study. There is one active treatment group and one vehicle treated group. Patients who meet the requirements of the inclusion/exclusion criteria at the screening visit are separated into a moderate stratum and a severe stratum based on the meibomian gland secretion quality. Within each stratum, patients are randomized to either 2.5% topical human recombinant IL-1Ra or vehicle in even allocations. There are a minimum of 20 patients in each treatment group in the moderate stratum and a minimum of 10 patients in each treatment group in the severe stratum. This study consists of 6 scheduled visits over four months (Table 2).

[164] Subjects who present signs or reported symptoms consistent with inflammatory disease affecting an ocular or adnexal tissue are further evaluated prior to treatment using the above-described Ocular Surface Disease Index (OSDI). Exemplary subjects are Male and female patients with signs and symptoms of posterior blepharitis (provided that not more than 7 glands are not expressible) with or without aqueous deficiency excluding those patients with end-stage lacrimal gland (Schirmer reading without anesthesia < 3 mm/5 min or if their dry eye disease is the result of destruction of conjunctival goblet cells or scarring). A subject is included in the following study if he or she meets the following criteria: male or female; at least 18 years of age; has not worn contact lenses for at least 2 weeks prior to the study and agrees to not wear contact lenses during study.; patient is in generally good & stable overall health. patient must have a diagnosis of posterior blepharitis as defined in Figure 5; a negative urine pregnancy test result for women of childbearing potential; women of childbearing potential must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry and for the duration of study participation; normal lid position and closure; ability to understand and

provide informed consent to participate in this study; and willingness to follow study instructions and likely to complete all required visits.

[165] Subjects are excluded if they had used topical steroids or the commercially-available drug, Restasis, within the past 2 weeks as well as tetracycline compounds (tetracycline, doxycycline, and minocycline) within the last month or isotretinoin (Accutane) within the past 6 months. Subjects who report any previous treatment with Anakinra (Kineret®) or any therapeutic agent targeted at IL-1 blockade are similarly excluded. Furthermore, a subject is excluded from the following study if he or she: has a history of Stevens-Johnson syndrome or ocular pemphigoid; has a history of eyelid surgery; has had intra-ocular surgery or ocular laser surgery within 3 months; has a history of microbial keratitis, including herpes; has active ocular allergies; has a corneal epithelial defect > $1mm^2$; has used topical steroids or Restasis within the past 2 weeks; has experienced any change in dosage of tetracycline compounds (tetracycline, doxycycline, and minocycline) within the last month; has used isotretinoin (Accutane) within the past 6 months; has had any previous treatment with Anakinra (Kineret®) or any therapeutic agent targeted at IL-1 blockade; is a pregnant or lactating woman; has signs of current infection, including fever and current treatment with antibiotics; has liver, renal, or hematologic disease; has a history of cancer; has used any other investigational drug.

[166] Under certain circumstances, subjects are withdrawn from the following study. The following criteria are used to determine when a subject must be removed or permitted to leave the study. Individuals are discontinued early from the study due to the following reasons, including, but not limited to: protocol violations, adverse events, lack of efficacy, pregnancy, and administrative reasons (e.g., inability to continue, lost to follow-up).

Screening Visit

[167] Prospective patients as defined by inclusion/exclusion criteria are considered for entry into this study. The study design and treatment regimen are discussed with each patient. Those wishing to participate are examined for entry into the study with the following exams:

- Medical and ophthalmic histories
- Patient questionnaire (OSDI) (see Example 1 and Figure 1)
- Best corrected visual acuity (BCVA) (Snellen chart)
- Fluorescein tear break-up time (TBUT) (see Example 2)
- Cornea and conjunctival staining (see Example 3
- Schirmer test without anesthesia (see Example 4)
- Schirmer test with anesthesia (see Example 4)
- Meibomian gland evaluation (see Example 5)

- Biomicroscopy
- Intraocular pressure
- Fundus examination

[168] To avoid the influence of one procedure on another, dry eye tests and ocular surface evaluation are done in the following sequence because the Schirmer test can disrupt tear film stability and cause false-positive ocular surface dye staining: measurement of tear film break-up time (TBUT), ocular surface dye staining pattern (fluorescein and lissamine green staining), Schirmer's test without and with anesthesia, and meibomian gland evaluation (Figure 6).

[169] After the eye examinations, each patient who qualifies to continue in the study (according to the inclusion/exclusion criteria) is instructed to instill one drop of the randomly assigned masked treatment three times a day in both eyes. The topical solution of 2.5% (25 mg/ml) concentration of Kineret is formulated and prepared from commercially available preservative-free solution of Kineret® (Amgen, Thousand Oaks, CA) by the MEEI hospital pharmacy using aseptic technique. For the control group, vehicle [Refresh Liquigel (1% Carboxymethylcellulose)] is used three times a day in both eyes. During the treatment phase, patients are instructed to instill 1 drop of study medication three times a day for 3 months; 1 drop in each eye upon waking in the morning, at noon, and at bedtime.

[170] To reduce the chance of systemic absorption of Kineret, patients are asked to put digital pressure on lacrimal ducts for five minutes. Patients are advised not use artificial tears or other topical medications 30 minutes before or 30 minutes after instilling the study medication to prevent dilution of the study medication. This study does not include blood sampling or any pharmacokinetic measures.

Compliance Visit

[171] Each patient returns for a compliance visit at 2 weeks (Table 2). At this visit, the investigator asks direct questions about patient compliance with the study treatment and adverse events. Patients can be discontinued from the study because of adverse events and protocol violations, but every effort is made to enhance compliance and maintain subjects on the treatment protocol.

Follow-up Visits

[172] To determine the safety and efficacy of topical IL-1Ra for management of posterior blepharitis, 5 follow-up visits (eye exam) are scheduled at day 1, week 2, 6, 12, and 16 (see

Table 2). Patients are instructed to strictly follow the study visit schedule. In each follow-up visit, the patient is asked to fill out the OSDI questionnaires (Figure 1). In addition to a comprehensive eye examination, tear function and ocular surface tests including TBUT, cornea and conjunctival staining tests, meibomian gland evaluation, and Schirmer tests, are performed.

Table 2: Schedule of Events and Procedures

Visit	1	2	3	4	5	6
Time Period	Screening Visit	Day 1 (Safety Visit)	Week 2 (Compliance Visit)	Week 6	Week 12	Week 16
Obtain Informed Consent	X					
Inclusion/exclusion criteria	X					
OSDI questionnaire	X		X	X	X	X
Medical & Ophthalmic History	X					
Pregnancy Test	X					
BCVA	X		X	X	X	X
TBUT	X		X	X	X	X
Cornea & Conj. Staining	X		X	X	X	X
Schirmer without Anesthesia	X		X	X	X	X
Schirmer with Anesthesia	X		X	X	X	X
Meibomian Gland Evaluation	X		X	X	X	X
Biomicroscopy	X	X	X	X	X	X
Intraocular Pressure	X		X	X	X	X
Funduscopy	X		X	X	X	X
Compliance Check		X	X	X	X	
Adverse Event Query		X	X	X	X	X

Concurrent Therapies

[173] Concurrent enrollment in another clinical investigational drug or device study is prohibited. The use of any concurrent medication, prescription or over-the-counter, is recorded along with the reason the medication is taken. During the study, all concomitant medication

treatment regimens, ocular hygiene treatments (i.e., lid scrubs and warm compresses), or insertion of punctal plugs are kept as constant as permitted by accepted medical practice.

[174] Using artificial tears is permissible at screening visits and during the study. However, concomitant use of artificial tears is monitored. At each study visit, patients are queried about the average number of times they used artificial tears each day during the past week and the number of days during the past week when they did not use any artificial tears.

[175] Systemic and topical ophthalmic medications that could interfere with the response to study medications or the interpretation of the study results are prohibited during the study. This includes any systemic or topical steroid, cyclosporine, and tetracycline compound.

[176] When necessary for the treatment of patients, administration of a prohibited therapy is done with the safety of the study participant as the primary consideration. The administration of a prohibited medication or procedure is considered a protocol violation and the patient may be discontinued from the study.

[177] During the course of study, if the patient complains of mild to moderate form of ocular surface symptoms, more frequent use of artificial tears (Refresh®) is encouraged without unmasking the patient. If treatment with artificial tears is inadequate, or the patient develops a severe form of ocular surface disease and dry eye, for the safety and proper treatment of the subject, the investigator can unmask the subject's treatment assignment to determine which treatment has been assigned and institute appropriate follow-up care. However, the patient is kept in the study so that an "intention to treat" analysis can be performed.

Efficacy Measures

[178] Several signs of the efficacy of administration of therapeutic compounds of the invention are monitored. The objective signs are meibomian gland secretion quality, meibomian gland occlusion, tear break-up time, corneal and conjunctival staining, and Schirmer test (with and without anesthesia). The subjective endpoints are the OSDI questionnaire score. All these variables are carefully measured at baseline and all visits toward the end of follow up (Table 2).

[179] The following are non-limiting examples of primary efficacy variables: Meibomian gland secretion quality; Tear Break-up time; Cornea and Conjunctival staining score; and the OSDI

questionnaire score. Alternatively, or in addition, secondary efficacy variables are used to determine the therapeutic value of administration of compositions of the invention. Nonlimiting examples of secondary efficacy variables include: Meibomian gland occlusion; Schirmer test without anesthesia; Schirmer test with anesthesia. Primary and/or secondary efficacy variables are considered.

[180] In this study, the treatment with topical IL-1Ra is considered efficacious if the 2.5% solution shows a mean change from baseline (0-3 scale) for meibomian gland secretion quality of > 1 unit better than vehicle at the week-12 visit. Alternatively, the treatment with topical IL-1Ra is considered efficacious if the 2.5% solution shows a mean change from baseline in average score (0-5 scale) for corneal and conjunctival staining of > 1 unit better than vehicle at the week-12 visit.

Safety Measures

[181] The primary safety variable monitored is the occurrence of adverse events. The severity of each adverse event observed (ocular and systemic) is rated from mild (awareness of sign or symptom, but easily tolerated) to severe (incapacitating with inability to work or do usual activity). The relationship of the event to the study medication is assessed by the investigator as none, unlikely, possible, probable, or definite. Safety variables are evaluated at baseline and at all study visits.

[182] At each visit throughout the study, the investigator begins querying for adverse events by asking each patient a general, non-directed question such as "How have you been feeling since the last visit?" Directed questioning and examination is then done as appropriate. The investigator asks questions to subjects at each visit to determine if they have had any changes to the use of concomitant medications since the previous visit. A comprehensive eye examination including best-corrected visual acuity, measuring intraocular pressure, evaluation of the condition of the lid/lashes, conjunctiva, cornea, anterior chamber, iris/pupil, lens, vitreous, macula and optic nerve is performed. Any changes in the study eye from the baseline visit is recorded.

STATISTICAL PROCEDURES

Power and Sample Size Considerations:

Table 3. Estimated Prevalence for Anticipated Ordered Categories of Meibomian Quality Scores

Scenario			Meibomian
High	Moderate	Low	Score
0.20	0.28	0.40	0
0.28	0.32	0.28	1
0.32	0.25	0.20	2
0.20	0.20	0.12	3
Mean (SD) = 1.52 (1.02)	Mean (SD) = 1.32 (1.09)	Mean (SD) = 1.04 (1.04)	

[183] In order to estimate the power of the study, it is assumed that 50% of the subjects are randomized to topical IL1-Ra and 50% to vehicle. A conservative estimate can then be constructed of study power, according to Sullivan and D'Agostino (Sullivan, L.M. and D'Agostino, R.B. 2003. Stat Med. 22(8):1317-34), using a t-test comparison of the predicted distribution of primary endpoints within ordered categories. Power estimates using this method are conservative because the actual analysis uses data from two eyes while appropriately accounting for their correlation, which has been demonstrated to have greater power as compared to methods based on using the person as the unit of analysis.

[184] The work of Sullivan and D'Agostino indicates that the t-test performs well for the comparison of ordinal scales with 3 to 5 ordinal categories. Estimates of power are based on three scenarios (high, moderate, and low) for the anticipated distribution of scores in the placebo group. As displayed in Table 3 above, a mean score between 1.04 and 1.52 is anticipated, with a standard deviation between 1.02 and 1.09. A clinically meaningful difference is a reduction of 1 in the mean score, or approximately 1 standard deviation.

[185] Based on the two-sample t-test, with Bonferonni adjustment for multiple comparisons (four primary outcome variables) an observer would have ≥80% power to detect a mean difference of 1 standard deviation for sample sizes of 28, 30, and 28, per group, under the high, moderate, and low scenarios, respectively. As noted, actual power would be enhanced through use of scores from both eyes of study participants, with consideration of the correlation between fellow eyes in the analysis. Therefore, the sample size of N=30 per group was chosen.

Statistical Analysis:

[186] For efficacy variables and any other variables except for safety, all subjects are analyzed with the treatment to which they were randomized (the intent-to-treat population). For safety variables, subjects are analyzed with the treatment actually received (the safety population).

[187] The primary analysis for the proposed study is based on a standard intention-to-treat analysis with each study participant analyzed with respect to the randomized treatment assignment, regardless of eventual compliance. A secondary analysis may include imputation of missing data for select variables. A per-protocol analysis, disqualifying patients or patient visits, might also be done, but is not planned because observational analyses of actual treatment use could introduce bias if the pattern of use is in some way related to the outcome.

[188] Despite the randomized nature of the treatment assignments, in this relatively small sample of study subjects there may be imbalances with regard to potential confounding variables. Thus, as an initial step in the analysis, those assigned to active treatment versus those randomized to vehicle are compared with regard to demographic characteristics and potential confounding variables, using the non-parametric Wilcoxon rank sum test for continuous or ordinal variables, and chi-square or Fisher's exact tests for categorical variables.

[189] To assess the effect of topical IL-1Ra treatment, the distribution of a) meibomian gland secretion score, and b) corneal and conjunctival staining scores between patients assigned to topical IL-1Ra and those assigned to vehicle are compared using the stratified Wilcoxon rank sum test with variance correction for clustering effects as recently developed by Rosner and Glynn (Rosner, et al. 2003. Biometrics. 59(4): 1089-98). Based on simulation studies, analyses of ophthalmologic data that use the information from two eyes and appropriately account for their correlation have greater power than methods based on a single eye or the average of the two eyes (Rosner, et al. 2003. Biometrics. 59(4): 1089-98; Glynn, R.J. and Rosner, B. 1994. Stat Med. 13(10): 1023-36). This method uses large sample theory to incorporate clustering effects to ordinal outcomes such as the clinical scoring scales used here. It can be implemented with standard software (e.g. SAS PROC RANK), and provides a valid test for either balanced or unbalanced clustered data in the presence or absence of tied rankings in datasets in which there are $\geq$20 clusters per group. The test may be used in place of the cluster-mean procedure (e.g. as would result from analysis using SAS PROC MIXED), and provides unbiased p-values where the standard Wilcoxon test is inappropriate. These analyses are then extended to control for potential confounding by variables using the stratified version of the test. A logical cut-point for stratification of continuous variables would be the median level among the vehicle treated group.

[190] Prior to the development of these methods, studies have generally used the person as the unit of analysis, using either a composite score or data from one eye per subject. However,

information is potentially lost by collapsing eye-specific grades into a single person-specific grade.

[191] In secondary analyses, the effect of topical IL-1Ra on other outcomes such as the OSDI score and tear break up time is also explored. Similarly, these analyses use the stratified Wilcoxon test with variance correction.

[192] In general, a two-sided test with p-value less than or equal to 0.0125 is considered statistically significant. This level of significance was arrived at by dividing the overall type 1 error rate of 0.05 by 4, which is the number of comparisons in the primary analysis.

[193] Although patients are evaluated at multiple time points throughout the study, the primary endpoint is on the last observation while on treatment during the 3-month study period.

EXAMPLE 9: Effect of IL-1Ra on Intraocular Pressure (IOP)

[194] IL-1Ra was administered to one eye of wild type BALB/c mice and the mean intraocular pressure (IOP) of the both the treated and the non-treated (contralateral eye) were measured. Data from these experiments show that administration of IL-1Ra is sufficient to reduce IOP by a statistically significant amount over the course of one day, and particularly, over the duration of one night (Table 4, below, and Figure 3). IOP is a risk factor for the development of glaucoma. Importantly, the compositions and methods used were effective on wild type, or normal, subjects. As such, this example is proof-of-concept that the compositions and methods of the invention are effective for treating elevated intraocular pressure or ocular hypertension that has been caused by a variety of mechanisms, including, but not limited to IL-1-mediated inflammation.

Table 4. Effect of one drop of topical IL-1Ra (2.5%) on Intraocular pressure (IOP) during the Day (after 6 hours) and Overnight (after 12 hours) in BALB/c mice. Data are expressed as the mean IOP (mm Hg) ± SEM. *P* value is for treated eye versus the contralateral eye (paired t-test).

	N	Contralateral Eye	Treated Eye	Difference (Contralateral Eye – Treated Eye)	% Reduction	*P* value
Day (after 6 h)	5	9.1 ± 0.46	8.0 ± 0.27	1.1 ± 0.51	11.5 ± 0.05	0.095
Overnight (After 12 h)	5	13.7 ± 0.90	10.3 ± 0.75	3.4 ± 0.38	24.7 ± 0.02	0.0009

OTHER EMBODIMENTS

[195] 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.

[196] 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.

[197] 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 inhibiting or reducing the severity of an inflammatory disorder affecting the ocular and adnexal tissues, comprising locally administering to an ocular or adnexal tissue of a subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine.

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

3. The method of claim 1, further comprising identifying a subject characterized as suffering from an inflammatory disorder affecting the ocular and adnexal tissues.

4. The method of claim 3, wherein said identifying step comprises detection of a sign or symptom selected from the group consisting of epithelial overexpression of an inflammatory cytokine, vascular hyperplasia or thickening of lid margin, neovascularization of lid margin or corneal periphery, increase of leukocytes at an ocular surface, or overexpression of a matrix metalloprotease at an ocular surface and wherein said method inhibits or reduces the severity of at least one of said signs or symptoms.

5. The method of claim 1, wherein said inflammatory disorder comprises infectious blepharitis.

6. The method of claim 1, wherein said inflammatory disorder comprises non-infectious blepharitis.

7. The method of claim 1, wherein said method does not comprise administration of an antibiotic compound.

8. The method of claim 1, wherein said method comprises administration of both an antibiotic compound and a composition that inhibits binding of an inflammatory IL-1 cytokine to an IL-1 receptor.

9. The method of claim 1, 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.

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

11. The method of claim 1, 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.

12. The method of claim 1, wherein said composition is administered topically.

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

14. The method of claim 1, 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, carboxymethylcellulose (CMC), hyaluronic acid, cyclodextrin, and petroleum.

15. A composition comprising a composition that inhibits an activity of an inflammatory interleukin-1 cytokine, wherein said composition is in the form of a solid, a paste, a liquid, an ointment, a gel, an aerosol, a mist, a polymer, a film, an emulsion, or a suspension, and wherein said composition is present at a concentration of 0.1 - 10% (mg/ml).

16. The composition of claim 15, wherein said composition comprises a polypeptide comprising the amino acid sequence of SEQ ID NO: 15 or SEQ ID NO: 16.

17. A contact lens comprising a composition that inhibits an activity of an inflammatory interleukin-1 cytokine, wherein said composition is incorporated into or coated onto said lens.

18. A method for inhibiting or reducing the severity of an ocular inflammatory disorder, comprising locally administering to the ocular or adnexal tissue of a subject a composition that 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.

19. The method of claim 18, wherein said composition comprises a polynucleotide, a polypeptide, an antibody, or a small molecule.

20. The method of claim 18, wherein said composition comprises a morpholino antisense oligonucleotide, microRNA (miRNA), short hairpin RNA (shRNA), or short interfering RNA (siRNA).

21. The method of claim 18, wherein said composition is administered topically.

22. A device comprising a polymer and a bioactive composition incorporated into or onto said polymer, wherein said bioactive composition inhibits an activity of an inflammatory interleukin-1 cytokine, and wherein said device is incorporated into or onto an ocular or adnexal tissue.

23. The method of claim 1, wherein said method comprises administration of both a composition that inhibits binding of an inflammatory IL-1 cytokine to an IL-1 receptor and a second composition comprising one or more inflammatory antagonist(s).

24. The method of claim 23, wherein said second composition inhibits tumor necrosis factor alpha (TNFα), one or more interleukin cytokines, one or more member(s) of the vascular epithelial growth factor (VEGF) family, interferon-gamma, or one or more chemokines and their receptors.

25. The method of claim 23 wherein said second composition comprises etanerept/Embrel, infliximab/Remicade, or adalimumab/Humira.

26. The method of claim 23 wherein said second composition comprises and inhibitor of TNFα, IL-2, IL-4, IL-5, IL-6, IL-8, IL-12, IL-17, IL-18, IL-23, VEGF-A, VEGF-C, VEGFR-2, VEGFR-3, interferon-gamma, CCR1, CCR2, CCR5, CCR7, or CXCR3.

27. The method of claim 23 wherein said second composition comprises an immunosuppressant.

28. The method of claim 23 wherein said second composition comprises cyclosporin A or analogs thereof, a glucocorticoid, a cytostatic agent, an alkylating agent, a nitrogen mustard, cyclophosphamide, a nitrosourea, a platinum compound, an antimetabolic agent, methotrexate, a folic acid analog, azathioprine, mercaptopurine, a purine analog, a pyrimidine analog, an

inhibitor of protein synthesis, a cytotoxic antibiotic, dactinomycin, an anthracycline, mitomycin C, bleomycin, mithramycin, a polyclonal antibody, Atgam®, Thympglobuline®, an antibody against an antilymphocyte antigen, an antibody against an antithymocyte antigen, a monoclonal antibody, OKT3®, an antibody against the T-cell receptor, an antibody against IL-2, basiliximab/Simulect®, declizumab/Zenapax®, Tacrolimus/Prograf™/FK506, Sirolimus/Rapamune™/Rapamycin, interferon beta, interferon gamma, an opioid, a TNFα binding protein, mycophenolate, or FTY720.

29. A method for inhibiting or reducing the severity of elevated intraocular pressure, comprising identifying a subject with elevated intraocular pressure and locally administering to an ocular or adnexal tissue of said subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine.

30. A method for inhibiting or reducing the severity of elevated intraocular pressure, comprising identifying a subject with elevated intraocular pressure and locally administering to the ocular or adnexal tissue of a subject a composition that 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.

31. A method for reducing intraocular pressure, comprising identifying a subject suffering from or at risk of a condition associated with above-normal intra-ocular pressure and locally administering to said subject a composition that inhibits an activity of an inflammatory interleukin-1 cytokine.

32. The method of claim 31, wherein said condition is glaucoma.

33. The method of claim 1 or 18, wherein said inflammatory disorder comprises elevated intraocular pressure, ocular hypertension, or glaucoma.

34. The method of claim 3, 29, 30, or 31 wherein said identifying step comprises measuring the intraocular pressure and determining if said intraocular pressure is elevated above normal levels.

35. The method of claim 1, 18, 29, 30, or 31 wherein said composition further comprises a compound selected from the group consisting of prostaglandin analogs (such as latanoprost

(Xalatan), bimatoprost (Lumigan) and travoprost (Travatan)); topical beta-adrenergic receptor antagonists (such as timolol, levobunolol (Betagan), and betaxolol,); Alpha2-adrenergic agonists (such as brimonidine (Alphagan)); sympathomimetics (such as epinephrine and dipivefrin (Propine)); miotic agents (parasympathomimetics) (such as pilocarpine); carbonic anhydrase inhibitors (such as dorzolamide (Trusopt), brinzolamide (Azopt), acetazolamide (Diamox)); physostigmine; fish oil; omega 3 fatty acids, bilberries, vitamin E, cannabinoids, carnitine, coenzyme Q10, curcurmin, Salvia miltiorrhiza, dark chocolate, erythropoietin, folic acid, Ginkgo biloba, Ginseng, L-glutathione, grape seed extract, green tea, magnesium, melatonin, methylcobalamin, N-acetyl-L cysteine, pycnogenols, resveratrol, quercetin, and fludrocortisone.

FIGURE 1

Ocular Surface Disease Index (OSDI)

Circle the number in the box that best represents each answer.

Have you experienced any of the following during the last week:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light?	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Have problems with your eyes limited you in performing any of the following during the last week:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Have your eyes felt uncomfortable in any of the following situations during the last week:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?	4	3	2	1	0	N/A

Total score for answers 1 to 12 _____

Total number of questions answered _____
(Do not include questions answered N/A)

OSDI= (sum of scores)/(# of questions answered) _____

FIGURE 2

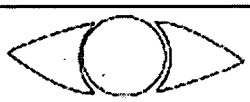
PANEL	Grade	Criteria
A 	0	Equal to or less than panel A
B 	I	Equal to or less than panel B, greater than A
C 	II	Equal to or less than panel C, greater than B
D 	III	Equal to or less than panel D, greater than C
E 	IV	Equal to or less than panel E, greater than D
>E	V	Greater than panel E

FIGURE 3

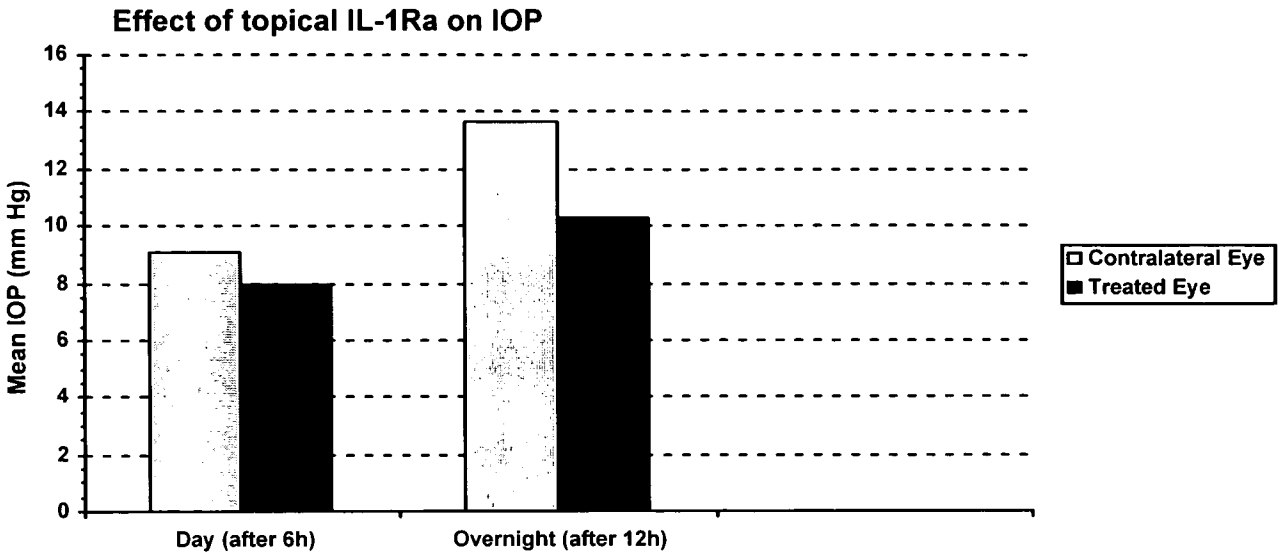

Effect of topical IL-1Ra on IOP
Mean IOP (mm Hg)
16
14
12
10
8
6
4
2
0
Day (after 6h)
Overnight (after 12h)
Contralateral Eye
Treated Eye

FIGURE 4

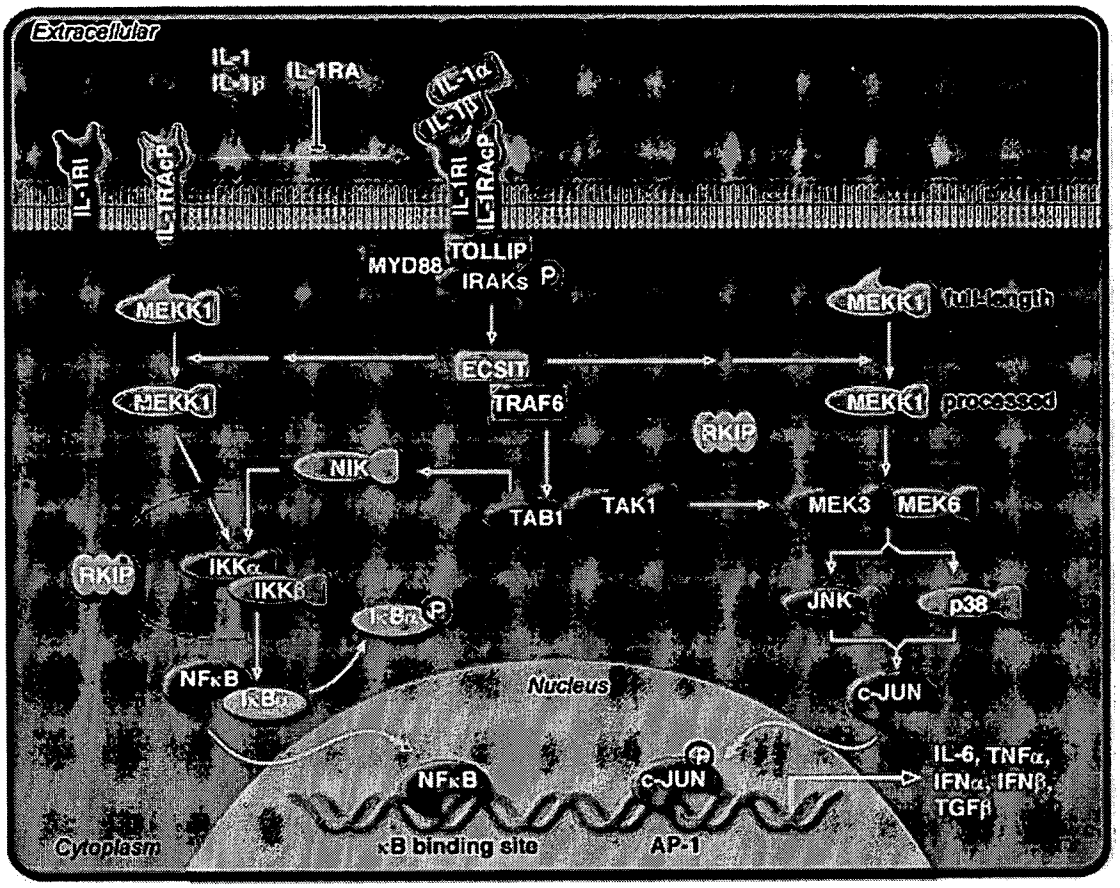

Extracellular
IL-1
IL-1β
IL-1RA
IL-1α
IL-1β
IL-1RI
IL-1RAcP
IL-1RI
IL-1RAcP
MYD88
TOLLIP
IRAKs
P
MEKK1
MEKK1
full-length
ECSIT
MEKK1
TRAF6
MEKK1
processed
RKIP
NIK
TAB1
TAK1
MEK3
MEK6
RKIP
IKKα
IKKβ
IκBα
P
JNK
p38
NFκB
IκBα
Nucleus
c-JUN
NFκB
P
c-JUN
IL-6, TNFα,
IFNα, IFNβ,
TGFβ
Cytoplasm
κB binding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

FIGURE 5

Definition of Meibomian Gland Dysfunction (Posterior Blepharitis)

Meibomian Gland Evaluation:
In the center of the lower lid, 10 adjacent central glands will be located on both sides and the glands will be expressed by applying a firm digital pressure at the base of the glands. The number of glands expressed for each eye will be documented.

Locate 10 central glands on the lower lid and circle the number of glands expressed for each eye.
1 2 3 4 5 6 7 8 9 10

The quality of secretion will be described as follows:

- Clear excreta or clear with small particles grade 0
- Opaque excreta with normal viscosity grade 1
- Opaque excreta with increased viscosity grade 2
- Secretions retain shape after expression grade 3

Lid and Lid Margin Evaluation: Lid margin vascular injection (erythema) is defined as a red discoloration, compared to the surrounding eyelid skin and will be graded as follows:

None	(0):	none
Mild	(1):	redness localized to a small region of the lid margin(s) or skin
Moderate	(2):	redness of most of the lid margin(s)
Severe	(3):	redness of most or all the lid margin(s) and skin
Very Severe	(4):	marked diffuse redness of both lid margins and skin

Presence or absence of tarsal telangiectasis will also be noted. Lid telangiectasia is defined as the presence of at least two blood vessels along the eyelid margin.

Conjunctiva (Palpebral and Bulbar): Bulbar conjunctival hyperemia will be graded as follows:

None	(0):	none
Mild	(1):	slight localized injection
Moderate	(2):	pink color, confined to palpebral or bulbar conjunctiva
Severe	(3):	red color of the palpebral and/or bulbar conjunctiva
Very Severe	(4):	marked dark redness of the palpebral and/or bulbar conjunctiva

Presence or absence of tarsal papillary hypertrophy will also be noted.

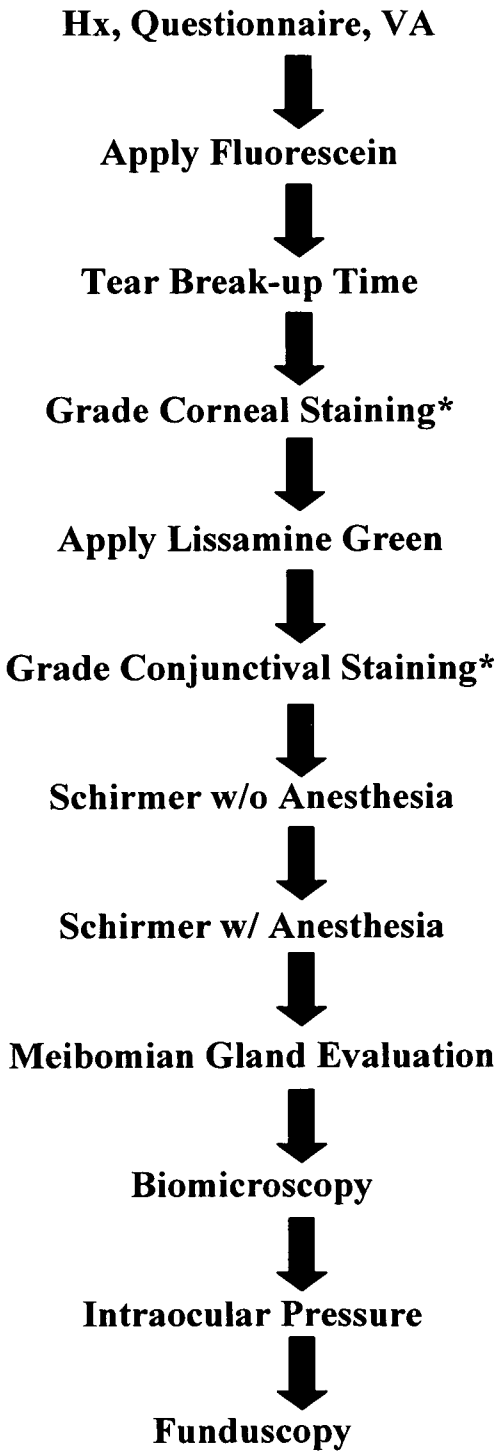
Posterior blepharitis will be diagnosed when in the presence of symptoms (itching, tearing, burning, and episodes of blurred vision), quality of meibomian gland secretion is $\geq$ grade 1 in at least one eye, and at least one of the following is present:

- Lid margin erythema
- Lid margin telangiectasia
- Conjunctival hyperemia or papillary reaction

FIGURE 6

Flow Diagram of Clinical Tests

To avoid the influence of one procedure on another, clinical tests, dry eye tests, and ocular surface evaluation will be done in the following sequence:



* Evaluate staining 2 minutes after dye instillation.