

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
16 July 2009 (16.07.2009)

PCT

(10) International Publication Number
WO 2009/089399 A2

(51) International Patent Classification:

C07K 16/28 (2006.01) **A61K 39/395** (2006.01)
C07K 16/18 (2006.01) **A61P 27/02** (2006.01)
C12N 15/11 (2006.01) **A61P 27/06** (2006.01)

(21) International Application Number:

PCT/US2009/030513

(22) International Filing Date: 9 January 2009 (09.01.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/020,159 10 January 2008 (10.01.2008) US

(71) Applicant (for all designated States except US): **BAUSCH & LOMB INCORPORATED** [US/US]; One Bausch & Lomb Place, Rochester, NY 14604-2701 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ZHANG, Jinzhong** [CN/US]; 7 Soho Circle, Pittsford, NY 14534 (US).
WARD, Keith, Wayne [US/US]; 5340 Lincoln Road, Ontario, NY 14619 (US). **VO, Toan** [US/US]; 65 Woodgreen Drive, Pittsford, NY 14534 (US).

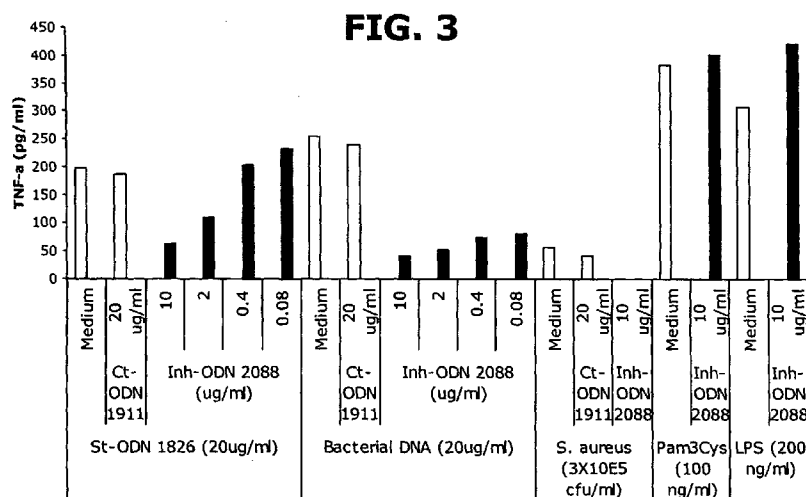
(74) Agents: **VO, Toan, P.** et al.; Bausch & Lomb Incorporated, One Bausch & Lomb Place, Rochester, NY 14604-2701 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: COMPOSITIONS COMPRISING TOLL-LIKE RECEPTOR OR CORECEPTOR ANTAGONISTS AND METHODS FOR OCULAR NEUROPROTECTION



(57) Abstract: Compositions for treating or controlling degeneration of at least a component of the human optic nerve system comprise an antagonist to a toll-like receptor, a coreceptor thereof, or a combination thereof. The compositions can also include an anti-inflammatory medicament. Such compositions can be administered to provide neuroprotection to a patient suffering from an ocular disease, such as glaucoma, AMD, DR, or retinitis pigmentosa.

WO 2009/089399 A2



Declaration under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

Published:

— *without international search report and to be republished
upon receipt of that report*

COMPOSITIONS COMPRISING TOLL-LIKE RECEPTOR OR CORECEPTOR ANTAGONISTS AND METHODS FOR OCULAR NEUROPROTECTION

BACKGROUND

The present invention relates to compositions and methods for effecting ocular neuroprotection. In particular, the present invention relates to compositions that comprise inhibitors of, or antagonists to, a Toll-like receptor ("TLR") or a TLR coreceptor, and to methods for effecting ocular neuroprotection using such compositions. In one aspect, the present invention relates to such compositions and methods for treating or controlling ocular neurodegenerative diseases.

Many pathological ocular conditions, if left untreated, often lead to vision loss and eventual blindness, which are the result of progressive death of optic nerve cells. One of such conditions is glaucoma. As defined by the American Academy of Ophthalmology, glaucoma is an optic neuropathy with characteristic structural damage to the optic nerve, associated with progressive retinal ganglion cell death, loss of nerve fibers, and visual field loss. On the basis of its etiology, glaucoma has been classified as primary or secondary. Primary glaucoma is an independent syndrome in adults and may be classified as either chronic open-angle or chronic (acute) angle-closure. Primary open-angle glaucoma is the most commonly occurring form of glaucoma, which appears to have no attributable underlying cause. Angle-closure glaucoma usually afflicts those persons having "shallow" angles in the anterior chamber and results from the sides (or angles) of the chamber coming together and blocking aqueous outflow through the trabecular meshwork. Secondary glaucoma, as the name suggests, results from pre-existing ocular diseases such as uveitis, intraocular tumor, or enlarged cataract.

Considering all types together, glaucoma occurs in about 2 percent of all persons over the age of 40 and may be asymptomatic for years before progressing to rapid loss of vision. The underlying causes of primary glaucoma are not yet well known. An intraocular pressure ("IOP") that is high compared to the population mean is a risk factor for the development of glaucoma. However, many individuals with high IOP do not have glaucomatous loss of vision. Conversely, there are glaucoma patients with normal IOP.

Therefore, continued efforts have been devoted to elucidate the pathogenic mechanisms of glaucomatous optic nerve degeneration.

It has been postulated that optic nerve fibers are compressed by high IOP, leading to an effective physiological axotomy and problems with axonal transport. High IOP also results in compression of blood vessels supplying the optic nerve heads ("ONHs"), leading to the progressive death of retinal ganglion cells ("RGCs"). See; e.g., M. Rudzinski and H.U. Saragovi, *Curr. Med. Chem.—Central Nervous System Agents*, Vol. 5, 43 (2005).

In addition, there is growing evidence that other molecular mechanisms also cause direct damage to RGCs: existence of high levels of neurotoxic substances such as glutamate and nitric oxide and pro-inflammatory processes. *Id.* At low concentrations, NO plays a beneficial role in neurotransmission and vasodilation, while at higher concentrations, it is implicated in having a role in the pathogenesis of stroke, demyelination, and other neurodegenerative diseases. R.N. Saha and K. Pahan, *Antioxidants & Redox Signaling*, Vol. 8, No. 5 & 6, 929 (2006). NO has been recognized as a mediator and regulator of inflammatory responses. It possesses cytotoxic properties and is produced by immune cells, including macrophages, with the aim of assisting in the destruction of pathogenic microorganisms, but it can also have damaging effects on host tissues. NO can also react with molecular oxygen and superoxide anion to produce reactive nitrogen species that can modify various cellular functions. R. Korhonen et al., *Curr. Drug Target—Inflam. & Allergy*, Vol. 4, 471 (2005). Furthermore, oxidative stress, occurring not only in the trabecular meshwork ("TM") but also in retinal cells, appears to be involved in the neuronal cell death affecting the optic nerve in primary open-angle glaucoma ("POAG"). A. Izzotti et al., *Mutat. Res.*, Vol. 612, No. 2, 105 (2006).

In addition, tumor necrosis factor- α ("TNF- α "), a pro-inflammatory cytokine, has recently been identified to be a mediator of RGC death. TNF- α and TNF- α receptor-1 are up-regulated in experimental rat models of glaucoma. In vitro studies have further identified that TNF- α -mediated RGC death involves the activation of both receptor-mediated caspase cascade and mitochondria-mediated caspase-dependent and caspase-independent components of cell death cascade. G. Tezel and X. Yang, *Expt'l Eye Res.*, Vol. 81, 207 (2005). Moreover, TNF- α and its receptor were found in greater amounts in

retina sections of glaucomatous eyes than in control eyes of age-matched normal donors. G. Tezel et al., *Invest. Ophthalmol. & Vis. Sci.*, Vol. 42, No. 8, 1787 (2001).

Regardless of the theory, glaucomatous visual field loss is a clinically recognized condition. There has been compelling evidence that such vision loss results from damage to optic nerve cells.

Retinitis pigmentosa, another back-of-the-eye disease, is the term for a group of inherited diseases that affect the retina, the delicate nerve tissue composed of several cell layers that line the inside of the back of the eye and contain photoreceptor cells. These diseases are characterized by a gradual breakdown and degeneration of the photoreceptor cells (the rod and cone cells), which result in a progressive loss of vision. Retinitis pigmentosa affects thousands of individuals in the United States. Together, rods and cones are the cells responsible for converting light into electrical impulses that transfer messages to the retinal ganglion cells which in turn transmit the impulses through the lateral geniculate nucleus into that area of the brain where sight is perceived. Retinitis pigmentosa, therefore, affects a different retinal cell type than those affected by glaucoma. Depending on which type of photoreceptor cell is predominantly affected, the symptoms vary, and include night blindness, loss of peripheral vision (also referred to as tunnel vision), and loss of the ability to discriminate color before peripheral vision is diminished. Symptoms of retinitis pigmentosa are most often recognized in adolescents and young adults, with progression of the disease usually continuing throughout the patient's life. The rate of progression and degree of visual loss are variable. As yet, there is no known cure for retinitis pigmentosa.

Age-related macular degeneration ("AMD"), another back-of-the eye disease, is a degenerative condition of the macula or central retina. It is the most common cause of vision loss in the over-50 age group. It is estimated that 50 million people worldwide suffer from AMD. Its prevalence increases with age and affects 15 percent of the population by age 55 and over 30 percent are affected by age 75. Macular degeneration can cause loss of central vision and make reading or driving impossible, but unlike glaucoma, macular degeneration does not cause complete blindness since peripheral vision is not affected. Macular degeneration can be detected during ophthalmologic examination.

Macular degeneration is classified as either dry (non-neovascular) or wet (neovascular). In its exudative or "wet" form, a layer of the retina becomes elevated with fluid, causing retinal detachment and wavy vision distortions. It has recently been discovered that mutations in two genes encoding proteins in the complement cascade, which is a part of the body's overall immune system, account for most of the risk of developing AMD. This complex molecular pathway is the body's first line of defense against invading bacteria, but if overactive, the pathway can produce tissue-damaging inflammation, which underlies the vision-destroying changes that particularly strike the macula. Proteins associated with immune system activity have been found in or near drusen, which are yellow deposits, in eyes with the dry form of AMD. Over time, the drusen grow as they accumulate inflammatory proteins and other materials, and the inflammation persists, causing additional damage to the retina and eventual vision loss. See; e.g., *Science*, Vol. 311, 1704 (2006).

Diabetic retinopathy ("DR"), another serious back-of-the eye disease, is a common complication of diabetes and a leading cause of blindness. The clinical hallmarks of DR include increased vascular permeability, leading to macular edema, and endothelial cell proliferation. It has become apparent that degenerative changes occur beyond the vascular cells of the retina. These include increased retinal cell apoptosis, loss of ganglion cell bodies, reduced thickness of the inner retina, increased glial cell reactivity, microglia activation, and altered glutamate metabolism. Together, these changes lead to continuing degeneration of the retina and irreversible deficits in vision. A.J. Barber, *Prog. Neuro-Psychopharmacol. & Biol. Psychiatry*, Vol. 27, 283 (2003). In addition, diabetes has an additive effect on neural apoptosis induced by increased IOP. Thus, diabetes is a risk factor of glaucomatous optic neuropathy by making retinal glia and neurons, including RGCs, susceptible to the additional stress of high IOP. M. Nakamura et al., *Ophthalmologica*, Vol. 219, 1 (2005).

Thus, it is now known that many serious back-of-the eye pathological conditions lead to loss of vision through progressive damage to various components of the optic nerve system. Consequently, current therapies attempt to prevent further damage to the remaining functioning cells of the optic nerve system. Pharmacological

intervention with IOP-lowering drugs has been prescribed to slow or stop optic nerve degeneration resulting from glaucoma.

Recently, α_2 -adrenergic receptor agonists have been noted to have neuroprotective effect on RGCs. See; e.g., E. Wolde-Mussie et al., *Invest. Ophthalmol. & Vis. Sci.*, Vol. 42, No. 12, 2849 (2001); M.P. Lafuente Lopez-Herrera et al., *Expt'l Neurol.*, Vol. 178, 243 (2002). It has been reported that injected brimonidine and clonidine, which are among the α_2 -adrenergic receptor agonists, delay the secondary degeneration of axons after a partial optic nerve crush in rats, and the neuroprotective effect could be blocked by α_2 -antagonists. A.T.E. Hartwick, *Optometry and Vision Science*, Vol. 78, No. 2, 85 (2001) (noting E. Yoles et al., *Ophthalmol. Vis. Sci.*, Vol. 40, 65 (1999)).

The continuing deterioration of vision in DR or AMD patients is currently treated with photocoagulation, in which laser flashes are used to burn the areas of retina containing leaky blood vessels. This treatment stops the course of the disease in about 50% of the cases and must be repeated in many patients.

Thus, the current treatment options for many serious ocular neurodegenerative diseases are limited and only attempt to prevent further deterioration of the diseases, but do not address the root causes that they may share.

Therefore, there is a continued need to provide other compounds and compositions that can provide effective neuroprotection to the optic nerve system. In addition, it is also desirable to provide methods for neuroprotection using such compositions.

SUMMARY

In general, the present invention provides compounds, compositions, and methods for providing neuroprotection to cells or components of a nervous system. In one embodiment, such a nervous system comprises the human optic nerve system.

In one aspect, the present invention provides compounds, compositions, and methods for treating or controlling degeneration of at least a component of the human optic nerve system.

In another aspect, such degeneration comprises a pathological result of DR, AMD (including dry and wet AMD), retinitis pigmentosa, glaucoma, or combinations thereof.

In still another aspect, a composition of the present invention comprises an inhibitor of an activity of, or an antagonist to, at least a toll-like receptor ("TLR") (such an inhibitor or antagonist hereinafter sometimes referred to as "TLR antagonist"); or an inhibitor of, or an antagonist to, a coreceptor of a TLR (such an inhibitor or antagonist hereinafter sometimes referred to as "TLR-coreceptor antagonist"), in an amount effective for treating or controlling degeneration of at least a component of a human optic nerve system in a subject.

In still another aspect, such a TLR is a human TLR.

In still another aspect, such a TLR is expressed in or on a cell or tissue associated with the human optic nerve system.

In yet another aspect, such a cell or tissue is associated with the retina or the optic nerve fiber.

In still another aspect, such an inhibitor of, or antagonist to, at least one human TLR or a coreceptor of a human TLR is capable of down regulating a TLR signaling pathway.

In yet another aspect, a composition of the present invention comprises a compound that is capable of inhibiting an activation of a human TLR signaling pathway.

In a further aspect, a composition of the present invention comprises: (a) a TLR antagonist, a TLR-coreceptor antagonist, or a combination thereof; and (b) an anti-

inflammatory medicament.

In yet another aspect, the present invention provides a method for treating or controlling degeneration of at least a component of an optic nerve system. The method comprises administering a composition to an affected eye, which composition comprises an inhibitor of, or an antagonist to, at least one human TLR; an inhibitor of, or an antagonist to, a coreceptor of a human TLR; or a compound that is capable of inhibiting an activation of a human TLR signaling pathway; or a combination thereof; in an effective amount for treating or controlling such degeneration.

Other features and advantages of the present invention will become apparent from the following detailed description and claims and the appended drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows ODN 2088 inhibition of neutrophil MIP-2 response.

Figure 2 shows ODN 2088 inhibition of neutrophil KC (keratinocyte-derived chemokine) response.

Figure 3 shows ODN 2088 inhibition of neutrophil TNF- α response.

Figure 4 ODN 2088 inhibition of neutrophil IL-6 response.

Figure 5 shows the effect of the inhibitory ODN 2088 on neutrophil infiltrate after a compromised mouse cornea has been exposed to stimulatory ODN 1826, bacterial DNA, Pam3Cys, or LPS.

Figure 6 shows ODN 2088 inhibition of corneal MIP-2, KC, and IP-10 response.

Figure 7 shows the effect of the inhibitory ODN (having sequence TTAGGG) on the TLR activation of human cell lines by Pam3Cys, flagellin, or CpGB.

DETAILED DESCRIPTION

As used herein, the term “control” also includes reduction, alleviation, amelioration, and prevention.

As used herein, the term “neuroprotection” means the rescue of at least some cells or components of a nervous system that are not directly damaged by the primary cause of a disease or injury, but would otherwise undergo secondary degeneration without therapeutic intervention. In one aspect, neuroprotection can lead to preservation of the physiological function of these cells or components. In one aspect, such a nervous system is the optic nerve system. The cells or components of the optic nerve system include those being involved or assisting in conversion of photon to neurological signal and the transmission thereof from the retina to the brain for processing. Thus, the main cells or components of the optic nerve system include, but are not limited to, pigment epithelial cells, photoreceptor cells (rod and cone cells), bipolar cells, horizontal cells, amacrine cells, interplexiform cells, ganglion cells, support cells to ganglion cells, and optic nerve fibers.

In general, the present invention provides compounds, compositions, and methods for providing neuroprotection to cells or components of a nervous system. In one embodiment, such a nervous system comprises the human optic nerve system.

In one aspect, the present invention provides compounds, compositions, and methods for treating or controlling degeneration of at least a component of the human optic nerve system.

In one aspect, a pharmaceutical composition of the present invention comprises an inhibitor of an activity of, or an antagonist to, at least a TLR (such an inhibitor or antagonist hereinafter sometimes referred to as “TLR antagonist”); or an inhibitor of, or an antagonist to, a coreceptor of a TLR (such an inhibitor or antagonist hereinafter sometimes referred to as “TLR-coreceptor antagonist”), in an amount effective for providing neuroprotection to cells or components of a nervous system.

In another aspect, a pharmaceutical composition of the present invention comprises a TLR antagonist or a TLR-coreceptor antagonist in an amount effective for treating or controlling an ocular neurodegenerative condition in a subject.

In still another aspect, such an ocular neurodegenerative condition comprises degeneration of a component of the human optic nerve system.

As used herein, the term “TLR antagonists” or “TLR-coreceptor antagonists” also includes compounds that inhibit or impede the expression of such receptor or coreceptors, respectively. In one embodiment, such an antagonist is present in the composition at concentrations such that the composition is capable of treating or controlling neurodegeneration in a subject.

In another aspect, such a TLR is a human TLR.

In still another aspect, such a TLR is expressed in or on a cell or tissue associated with the human optic nerve system.

It has been established that inflammation is an underlying component of a diverse range of neurodegenerative diseases, including those of the eye, and their associated neuropathology. In one aspect, increasing evidence suggests that activated glial cells, including microglia, are a key causative factor in ocular neuropathology.

It has been discovered that cellular Toll-like receptors (“TLRs”) play a central role in initiating and maintaining the inflammatory response of the body to foreign materials. TLRs potentially can also be activated by ligands (e.g., heat shock protein 60 (“hsp60”), heat shock protein 70 (“hsp70”), glucose-regulated proteins, or high-mobility group protein 1) that are generated endogenously under effects of stressors. Heat shock proteins are also released from cells undergoing necrosis, enter the blood stream, and affect distant targets. To date, at least eleven mammalian TLRs (TLR1-TLR11), ten in human, have been identified, and ligands that activate some of these TLRs have been ascertained. K. Takeda et al., *Annual Rev. Immunol.*, Vol. 21, 335 (2003). TLRs have been identified in donor ocular tissues and cultured cells of the retinal pigment epithelium (“RPE”) and cornea. The normal human retina, uvea, and sclera are known to express

TLR4 mRNA. In addition, TLR2, TLR4, and TLR9 mRNA and proteins were identified in the conjunctiva of healthy subjects. S. Bonini et al., *Ophthalmol.*, Vol. 112, 1528 (2005). Similarly, cultured cells of the corneal epithelium express TLR4 and TLR5, whereas cells of the RPE highly express TLR3 as well as TLR1, TLR2, TLR4, TLR7, TLR9, and TLR10.

TLRs play a crucial role in the activation of several immune cell types, such as dendritic cells, neutrophils, eosinophils, basophils, monocytes, macrophages, and mast cells, leading to synthesis and release of a wide range of pro-inflammatory cytokines and chemokines. Excessive or chronic production of such pro-inflammatory compounds can be very damaging to surrounding healthy tissues. Ligand binding to TLRs can also induce apoptosis. B. Salaun et al., *Eur. J. Immunol.*, Vol. 37, 3311 (2007).

The various TLRs have evolved to recognize different structural features of the diverse microorganisms, referred to as “pathogen-associated molecular patterns” (or “PAMPs”), which are highly conserved across species of microorganisms. Due to this ready recognition of PAMPs, the innate immune system can mount a rapid host defense response to invading pathogens. For example, TLR1 recognizes tri-acyl lipopeptides of bacteria and *Mycobacteria*. TLR2 recognizes lipoproteins and lipopeptides of a variety of Gram-negative bacteria, peptidoglycan and lipoteichoic acid of Gram-positive bacteria, lipoarabinomannan of *Mycobacteria*, and several types of atypical lipopolysaccharides (“LPSs”) of *Leptospira interrogans* and *Porphyromonas gingivalis*. TLR3 recognizes double-stranded RNA (“dsRNA”) of viruses. TLR4 recognizes LPSs, which are outer-membrane components of Gram-negative bacteria and are structurally different from the atypical LPSs recognized by TLR2. TLR5 recognizes flagellin of Gram-negative bacteria. TLR6 recognizes di-acyl lipopeptides. *Id.* Human TLR7 and TLR8 recognize imidazoquinoline compounds, which are structurally related to guanosine nucleoside. Thus, they are predicted to recognize nucleic acid-like structure of viruses or bacteria. K. Takeda et al., *Int. Immunol.*, Vol. 17, No. 1, 1 (2005). In fact, TLR8 recently has been indicated to recognize single-stranded RNA of viruses (“ssRNA”). TLR9 recognizes the unmethylated CpG motifs of bacterial DNA. To date, ligands of TLR10 have not been ascertained. Additional TLRs may be discovered in the future as knowledge of the immune system continues to expand. TLR expression and function have been

demonstrated in the eye. See; e.g., J.H. Chang et al., *Br. J. Ophthalmol.*, Vol. 90, 103 (2006).

It has been shown that some TLRs act in concert with other TLRs or coreceptors (such as CD14 or MD-2) to initiate intracellular inflammatory cascades, which have the ultimate goal of elimination of the foreign materials from the body. Among the most prominent and best characterized of these cascades is that leading to the activation of the transcription factor NF- κ B, which, in turn, activates the genes for production of many pro-inflammatory factors (such as TNF- α , IL-1, and IL-12). In addition, TLRs can also initiate mitogen-activated protein kinase ("MAPK") signaling cascades and thus activate other transcription factors, including activator protein 1 ("AP-1") and Elk-1. G. Zhang et al., *J. Clin. Invest.*, Vol. 107, No. 1, 13 (2001).

Therefore, exposure to materials that are not normally present in the body elicits an initial innate immune response in otherwise healthy persons, resulting in the recruitment of immune cells to sites of such exposure. These immune cells further synthesize and release pro-inflammatory cytokines such as IL-1 β , IL-3, IL-5, IL-6, IL-8, TNF- α (tumor necrosis factor- α), GM-CSF (granulocyte-macrophage colony-stimulating factor), and MCP-1 (monocyte chemotactic protein-1). These released cytokines then further attract more immune cells to the affected site, amplifying the response of the immune system to defend the host against the foreign pathogen or insult. For example, IL-8 and MCP-1 are potent chemoattractants for, and activators of, neutrophils and monocytes, respectively, while GM-CSF prolongs the survival of these cells and increases their response to other pro-inflammatory agonists. TNF- α can activate both types of cell and can stimulate further release of IL-8 and MCP-1 from them. IL-1 and TNF- α are potent chemoattractants for T and B lymphocytes, which are activated to produce antibodies against the foreign pathogen.

Although an inflammatory response is essential to clear foreign materials from the site of invasion, a prolonged or overactive inflammatory response can be damaging to the surrounding tissues. For example, inflammation causes the blood vessels at the infected site to dilate to increase blood flow to the site. As a result, these dilated vessels become leaky. After prolonged inflammation, the leaky vessels can produce serious edema in, and impair the proper functioning of, the surrounding tissues (see; e.g.,

V.W.M. van Hinsbergh, *Arteriosclerosis, Thrombosis, and Vascular Biology*, Vol. 17, 1018 (1997)). In addition, a continued dominating presence of macrophages at the site of invasion continues the production of toxins (such as reactive oxygen species) and matrix-degrading enzymes (such as matrix metalloproteinases) by these cells, which are injurious to both the pathogen and the host's tissues. An unchecked inflammatory condition can eventually lead to death of the tissue. Therefore, an inappropriately vigorous activation of the immune system in response to non-infectious foreign materials should be controlled to limit the unintended damages to an otherwise healthy tissue.

Microglia are the resident innate immune cells in the central nervous system. Early microglia activation in the retina is a common response to ocular infections, autoimmune mechanisms, neuronal injury, ischemia, and metabolic as well as hereditary retinopathies. Activated microglia exhibit strongly enhanced proliferation, phagocytosis, and production of many different bioactive molecules, which include IL-1, IL-6, TNF- α , NO, PGE₂, MCP-1, MCP-3, RANTES, MIP-1 α , M-CSF, and superoxide that are toxic to neurons and are all associated with progressive neurodegeneration. T. Langman, *J. Leucocyte Biol.*, doi :10.1189/jlb.0207114 (2007); M.L. Block et al., *Nature Rev. Neuroscience*, Vol. 8, 57 (2007). It becomes increasingly evident that the TLRs, which are broadly expressed on microglia, can react to aberrant endogenous ligands in neuronal tissues. Gangliosides, hyaluronic acid, heparan sulfate, and heat shock proteins carry damage-associated molecular patterns and thereby can elicit microglia activation. Microglial TLR4 induction has been detected in the retina. Furthermore, TLR4, along with TLR2, in turn can trigger microglia apoptosis. T. Langman, *supra*. In addition, TLR8 functions as a negative regulator of neurite outgrowth and inducer of neuronal apoptosis, thus can act to inhibit neuronal repair or to exacerbate neurodegeneration. Y. Ma et al., *J. Cell Biol.*, Vol. 175, No. 2, 209 (2005). There is also evidence that TLR3 signaling occurs in retinal vascular endothelial cells and leads to retinal tissue damage in patients with idiopathic uveitis and Behçet disease. M.T. Lee et al., *Clin. & Expt. Immunol.*, Vol. 147, 71 (2006). Retinal pigment endothelial ("RPE") cells have been shown to express TLR4. Given that RPE cells have a major immunological role at the blood-retina barrier, over-expression of TLR4 and its hyperactivity in the retinal pigment epithelium implicate its potential role for the pathogenesis of various retinal diseases.

There has been evidence that over-expression of TLR4 participates in the pathogenesis of AMD. S. Zarepari et al., Vol. 14, No. 11, 1449 (2005).

Therefore, in one aspect, the present invention provides compositions and methods for treating or controlling an ocular neurodegenerative condition in a subject.

In another aspect, such compositions provide ocular neuroprotection in the subject through inhibiting or antagonizing activity of one or more human TLRs.

In still another aspect, a composition of the present invention comprises an inhibitor of, or antagonist to, at least one human TLR or a coreceptor of a human TLR, or a compound capable of down regulating a TLR signaling pathway.

In still another aspect, a composition of the present invention comprises a compound that is capable of inhibiting an activation of a human TLR signaling pathway.

In yet another aspect, a composition of the present invention comprises a TLR antagonist or a TLR-coreceptor antagonist and an anti-inflammatory medicament. Preferably, such an anti-inflammatory medicament comprises a nonsteroidal compound.

In still another aspect, a TLR antagonist or TLR-coreceptor antagonist, included in a composition of the present invention, inhibits the binding of ligands to such TLR or TLR coreceptor, respectively, which ligands are capable of activating such TLR or coreceptor, or the binding of such coreceptor to such TLR.

In yet another aspect, said at least one human TLR is selected from the group consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, and combinations thereof.

In still another aspect, said at least one human TLR is selected from the group consisting of TLR2, TLR3, TLR4, TLR8, TLR9, and combinations thereof.

In still another aspect, said at least one human TLR is selected from the group

consisting of TLR3, TLR4, TLR8, and combinations thereof.

In a further aspect, said coreceptor of a human TLR is selected from the group consisting of CD14, MD-2, and a combination thereof. CD14 has been shown to be an essential coreceptor for TLR2 and TLR4 activation due to the required formation of the receptor complex comprising CD14 and TLR2 or TLR4 before the signaling cascades involving these TLRs are initiated. G. Zhang et al., *J. Clin. Invest.*, Vol. 107, No. 1, 113 (2001); R. Arroyo-Espliguero et al., *Heart*, Vol. 90, 983 (2004). Growing evidence has suggested that an association of MD-2, a lipid binding protein, with the leucine-rich repeats ("LRRs") of the extracellular domain of TLR4 or TLR2 is necessary for the initiation of the signaling cascade involving this TLR by LPS components of bacteria. See; e.g., T.L. Gioannini et al., *PNAS*, Vol. 101, No. 2, 4186 (2004); R. Dziarski et al., *J. Immunol.*, Vol. 166, 1938 (2001).

In one aspect, a composition of the present invention comprises an anti-human antibody of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, CD14, MD-2, or combinations thereof. Many of these antibodies are available from eBioscience, San Diego, California. In one embodiment, such an antagonist is a monoclonal antibody. In another embodiment, such an antagonist is a recombinant antibody of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, CD14, MD-2, or combinations thereof.

In another aspect, a composition of the present invention comprises a soluble form of an extracellular domain of a TLR ("sTLR") that recognizes a moiety of a compound not normally present in a healthy body (a "foreign moiety"). By binding to a foreign moiety, a sTLR renders it unavailable for binding to the corresponding TLR and activating the signaling cascade involving the same TLR. Soluble TLRs are available from, for example, eBioscience, San Diego, California. These molecules may be cleaved into smaller fragments, for example, using enzymatic digestion, and those fragments that recognize a particular foreign moiety at high affinity may be identified through binding assays that are well known in the art.

In still another aspect, a composition of the present invention comprises a soluble form of a CD14-binding extracellular domain of TLR4 ("sTLR4"), a soluble form of CD14 molecule ("sCD14"), or a soluble form of MD-2 ("sMD-2"). Such sTLR4 binds

to CD14 and prevents it from binding to membrane-bound TLR4 and assisting in activating the signaling cascade involving the same. On the other hand, sCD14 and sMD-2 bind to LPS components of bacteria and prevent its binding to TLR4 and subsequent activation of this TLR. Soluble forms of extracellular domain of TLR4 and MD-2 have been shown to be effective in inhibiting LPS-elicited IL-8 release from U937 cells and NF- κ B activation. H. Mitsuzawa et al., *J. Immunol.*, Vol. 177, 8133 (2006). Soluble CD14 and MD-2 are available from, for example, IMGENEX, Corp., San Diego, California.

In another aspect, a composition of the present invention comprises a TLR-inhibiting oligodeoxynucleoside ("ODN") that comprises at least three consecutive guanosine deoxynucleotides. In one embodiment, a composition of the present invention comprises a TLR-inhibiting ODN that comprises at least a GGG ("G-triplet") or GGGG ("G-tetrad") motif. In another embodiment, a composition of the present invention comprises a TLR-inhibiting single-stranded ODN that comprises multiple TTAGGG motifs (SEQ. NO. 1) or a sequence of TCCTGGCGGGGAAGT (SEQ. NO. 2). SEQ. NO. 1 is ubiquitously found in human telomeres. SEQ. NO. 2 is a synthetic ODN, known as ODN 2088, available from InvivoGen, San Diego, California. These ODNs have been shown to block the colocalization of CpG DNA, which is ubiquitously found in bacterial products, with TLR9 within endosomal vesicles. I. Gursel et al., *J. Immunol.*, Vol. 171, 1393 (2003); L.L. Stunz et al., *Eur. J. Immunol.*, Vol. 171, No. 3, 1212 (2002). Preferably, a TLR-inhibiting ODN comprises at least one G-tetrad. Alternatively, a TLR-inhibiting ODN comprises one, two, three, four, or more G-tetrads. When a TLR-inhibiting ODN comprises more than one G-tetrad, the G-tetrads can be arranged contiguously. Alternatively, the G-tetrads can be separated by one or more different deoxynucleotides, such as one, two, three, four, five, ten, fifteen, twenty, or more deoxynucleotides. In one embodiment, the G-tetrads are separated by fewer than 20 other deoxynucleotides. Other suitable inhibiting ODNs include the synthetic ODNs having the sequences: TCCTAACGGGGAAGT (SEQ. NO. 3), TCCTGGAGGGGTTGT (SEQ. NO. 4) (see O. Duramad et al., *J. Immunol.*, Vol. 174, 5193 (2005)), TCCTGGCGGGCAAGT (SEQ. NO. 5), TCCTGGCGGGTAAGT (SEQ. NO. 6), TCCTGGCGGGAAAGT (SEQ. NO. 7), TCCTGCAGGGTAAGT (SEQ. NO. 8) (see L.L. Stunz et al., *Eur. J. Immunol.*, Vol. 32, 1212 (2002)).

In one embodiment, ODNs comprising one or more G-tetrads can self-assemble into four-stranded helices stabilized by planar Hoogsteen base-paired quartets of guanosine. Such four-stranded ODNs are also within the scope of the present invention.

In other embodiments, a composition of the present invention comprises one or more inhibiting ODNs having SEQ. NO. 21 – SEQ. NO. 29: TCCTGGCGGGGAAGT (SEQ. NO. 21); GCCTGGCGGGGAAGT (SEQ. NO. 22); ACCTGGCGGGGAAGT (SEQ. NO. 23); CCCTGGCGGGGAAGT (SEQ. NO. 24); TCCCGGCGGGGAAGT (SEQ. NO. 25); TCCAGGCGGGGAAGT (SEQ. NO. 26); CCTGGCGGGGAAGT (SEQ. NO. 27); TCCTAGCGGGGAAGT (SEQ. NO. 28); and TCCTGGAGGGGAAGT (SEQ. NO. 29). These inhibiting ODNs are disclosed in US Patent Application Publication 2005/0239733, which is incorporated herein by reference, and are shown to inhibit activity of at least one of TLR8 and TLR9.

In another embodiment, a composition of the present invention comprises a TLR-inhibiting ODN that comprises two, three, four, five, or more TTAGGG motifs. In a preferred embodiment, a TLR-inhibiting ODN comprises four TTAGGG motifs. In another embodiment, four TTAGGG motifs are arranged contiguously.

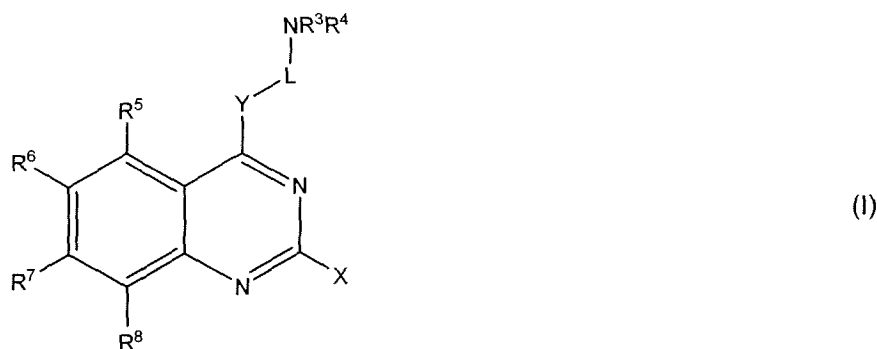
In still another embodiment, a composition of the present invention comprises a TLR-inhibiting ODN that comprises two, three, four, five, or more repeats of any one of SEQ. NO. 2 – SEQ. NO. 8, SEQ. NO. 21 – SEQ. NO. 29, or a combination thereof.

In yet another aspect, a composition of the present invention comprises an effective amount of chloroquine, hydroxychloroquine, quinacrine, 9-aminoacridine, 4-aminoquinoline, or a mixture thereof, for inhibiting the activity of TLR9. These compounds have been shown to block the immunostimulatory action of CpG ODN and induce remission of rheumatoid arthritis (“RA”) and systemic lupus erythematosus (“SLE”). R.N. Bhattacharjee et al., *Mini Rev. Med. Chem.*, Vol. 5, 287 (2006); D.E. Macfarlane et al., *J. Immunol.*, Vol. 160, 1122 (1998). Specifically, chloroquine has been used clinically for the treatment of RA and SLE. Chloroquine blocks TLR9-dependent signaling through inhibition of the pH-dependent maturation of endosomes by acting as a basic substance to neutralize acidification in the vesicles. H. Hacker et al., *EMBO J.*, Vol. 17, 6230 (1998). Therefore, chloroquine can act in a composition of the present invention

as a TLR9 immunomodulatory agent.

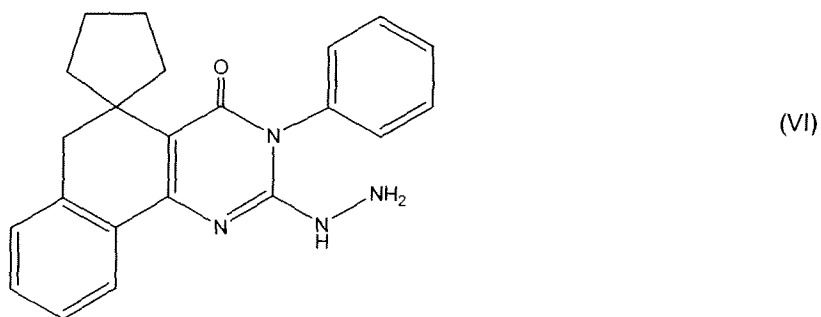
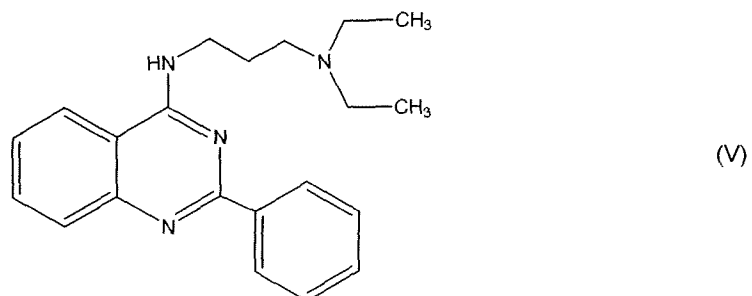
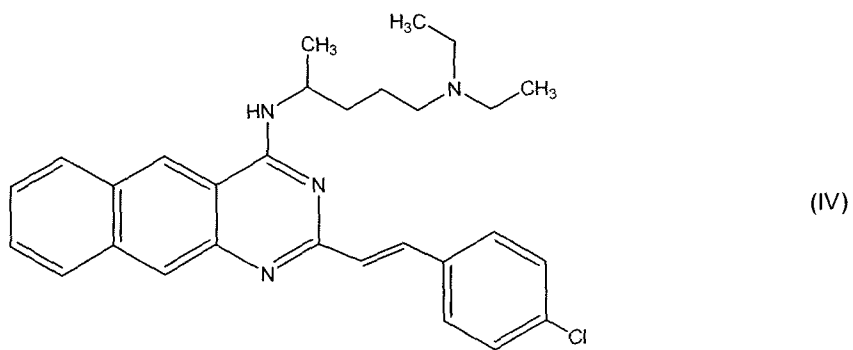
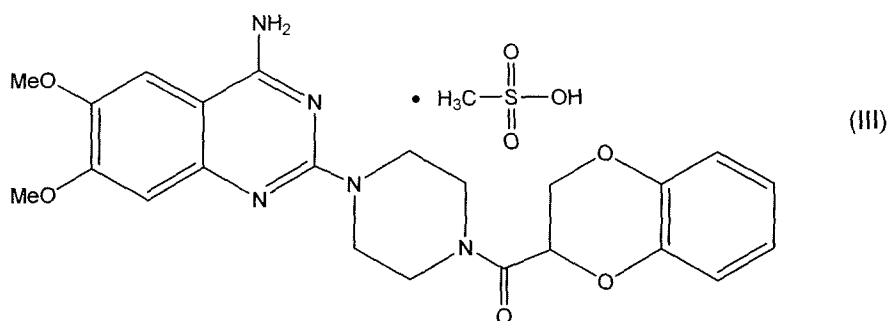
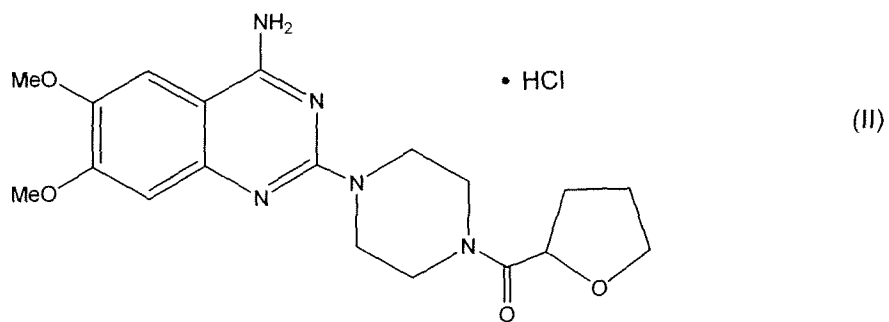
In a further aspect, a composition of the present invention comprises an inhibitor to an expression of a human TLR. In one embodiment, such an inhibitor comprises a ligand of vitamin D receptor ("VDR") or a VDR agonist. In another embodiment, such a ligand of VDR or VDR agonist comprises vitamin D or a vitamin-D analogue. A suitable vitamin-D analogue is calcipotriol ((1*R*,3*S*)-5-[2-[(1*R*,3*aR*,7*aS*)-1-[(2*S*)-5-cyclopropyl-5-hydroxy-pent-3-en-2-yl]-7*a*-methyl-2,3,3*a*,5,6,7-hexahydro-1*H*-inden-4-ylidene]ethylidene]-4-methylidene-cyclohexane-1,3-diol). In still another embodiment, such a ligand is vitamin D₂ (ergocalciferol or calciferol) or vitamin D₃ (1,25-dihydroxycholecalciferol or calcitriol). In yet another embodiment, such a ligand is vitamin D₃. It has been accepted that vitamin D₃ is a bona-fide hormone involved in cell growth, differentiation, and immunomodulation. The active form of vitamin D mediates immunological effects by binding to nuclear VDR, which is present in virtually all tissues and cell types, including both innate and acquired immune cells. Y.Y. Yee et al., *Mini Rev. Med. Chem.*, Vol. 5, 761 (2005). Activated VDR can antagonize the action of transcription factors NF-AT and NF- κ B. *Id.* Thus, activated VDR or vitamin D₃ have been shown to inhibit the expression of pro-inflammatory cytokines, such as IL-2, IL-6, IL-8, IL-12, TNF- α , IFN- γ , and GM-CSF. In addition, vitamin D₃ enhances the production of IL-10 and promotes dendritic cell ("DC") apoptosis, and, thus, inhibits DC-dependent activation of T cells. E. van Etten et al., *J. Steroid Biochem. Mol. Biol.*, Vol. 97, No. 1-2, 93 (2005). Moreover, there is evidence indicating that vitamin D₃ diminishes the expression of TLR2 and TLR4 in monocytes. K. Sadeghi et al., *Eur. J. Immunol.*, Vol. 36, 361 (2006). Thus, vitamin D₃ or its analogues, or other VDR agonists can reduce the sensitization of these cells to MEMs, such as lipoproteins and lipopeptides of a variety of Gram-negative bacteria, peptidoglycan and lipoteichoic acid of Gram-positive bacteria, lipoarabinomannan of *Mycobacteria*, and other atypical lipopolysaccharides. Consequently, application of a composition of the present invention containing a vitamin D, a vitamin-D analogue, or a VDR agonist can reduce the risk of development, or the severity, of an inappropriate immune response. As used herein, the term "inappropriate immune response" means a response of the body's immune system to an inciting stimulus, which response is at an unwanted high level that results in a pathological condition.

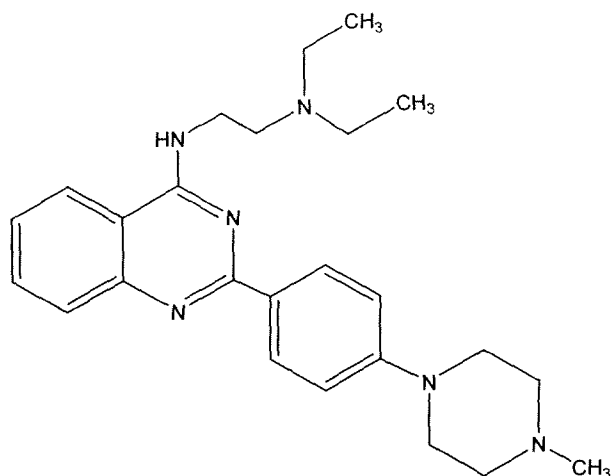
In another aspect, an antagonist to one or more TLR receptors included in a composition of the present invention comprises a quinazoline derivative, as disclosed in US Patent Application Publication 2005/0119273, which is incorporated herein by reference. Such a quinazoline derivative has a general Formula I.



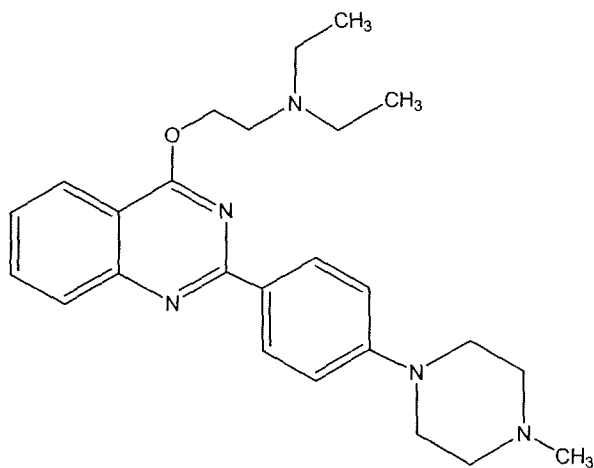
wherein X is a substituted or unsubstituted aryl, alkyl, heterocyclic, or styryl group, optionally attached to the quinazoline by a nitrogen, oxygen, or sulfur atom or by a SO or SO₂ group; Y is absent or is an oxygen atom, a sulfur atom, CR⁹R¹⁰, or NR¹¹, wherein R⁹, R¹⁰, and R¹¹ are each independently a hydrogen atom or an alkyl, alkenyl, or aryl group, wherein any one of R⁹, R¹⁰, and R¹¹ optionally is combined with R³ or R⁴ to form a heterocycle; L is absent or is a hydrogen atom, an alkyl or alkenyl group containing from 1 to 10 carbons, or an aryl group; R³ and R⁴ are each independently a hydrogen atom or an alkyl, alkenyl, or aryl group, wherein R³ and R⁴ optionally are combined to form a heterocycle; and R⁵, R⁶, R⁷, and R⁸ are each independently a hydrogen atom, a halogen atom, or an alkyl, alkenyl, aryl, heterocyclic, nitro, cyano, carboxy, ester, ketone, amino, amido, hydroxy, alkoxy, mercapto, thio, sulfoxide, sulfone, or sulfonamido group, wherein any pair of R⁵, R⁶, R⁷, and R⁸ which are adjacent one another optionally are combined to form a heterocycle or a carbocycle.

Non-limiting examples of such quinazoline derivatives, which are effective in inhibiting one or more of TLR3, TLR7, TLR8, and TLR9, include:



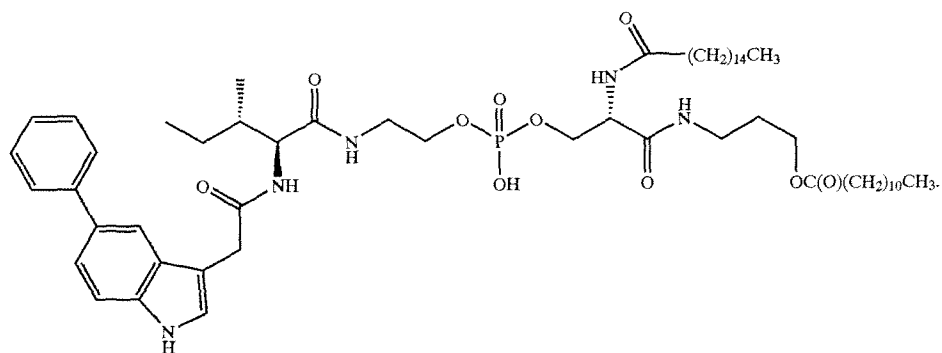


(VII)

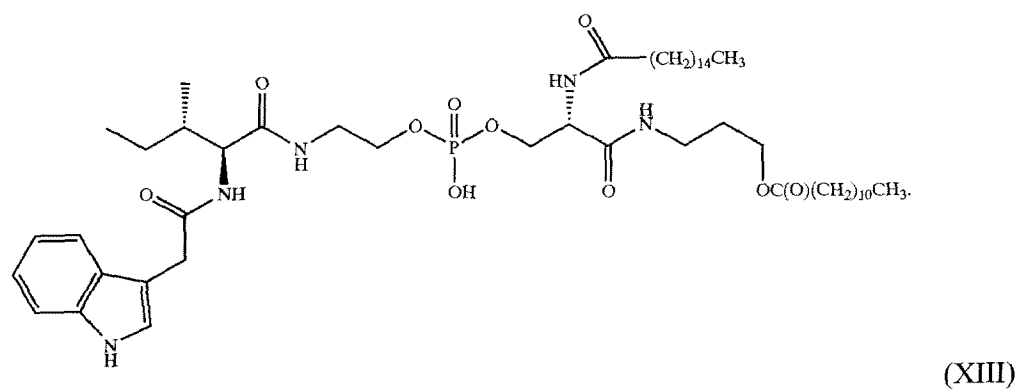
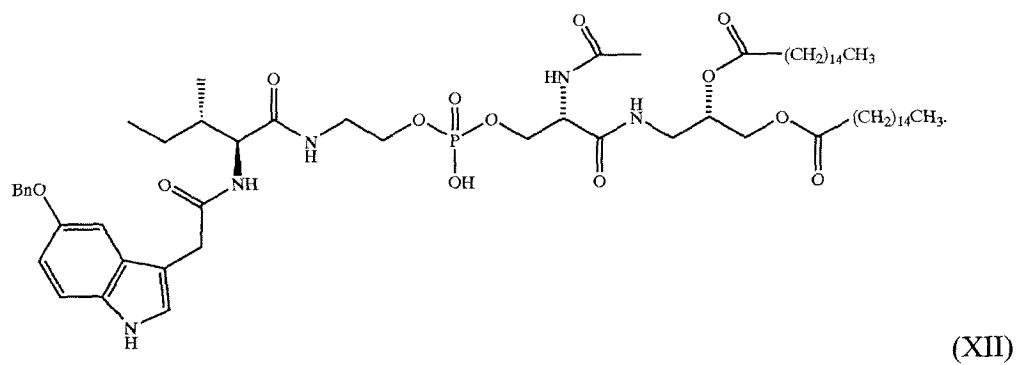
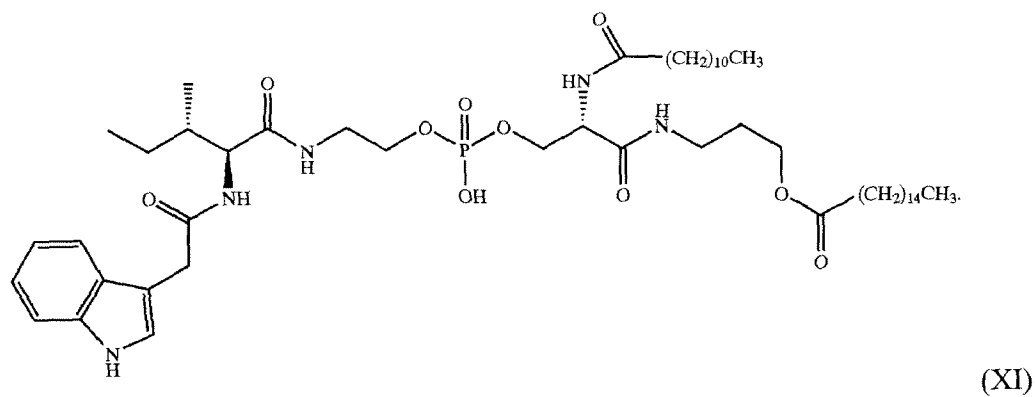
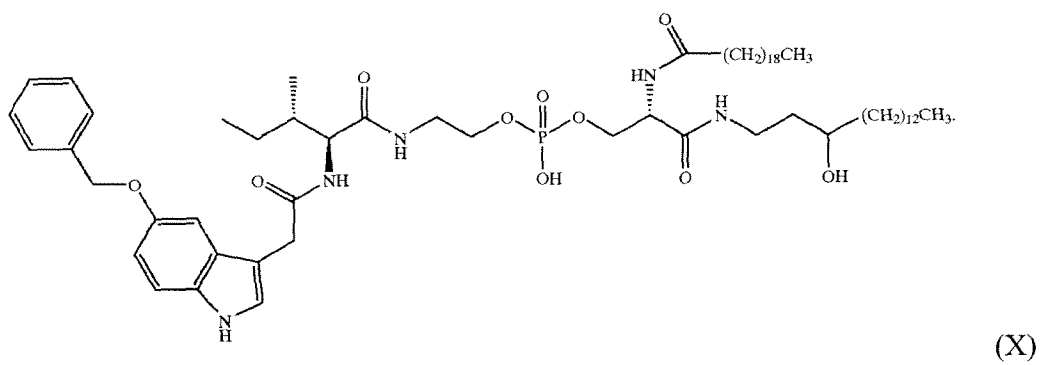


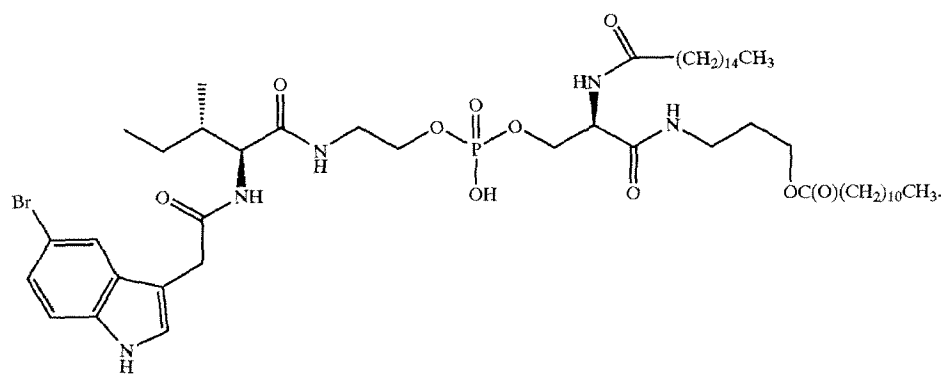
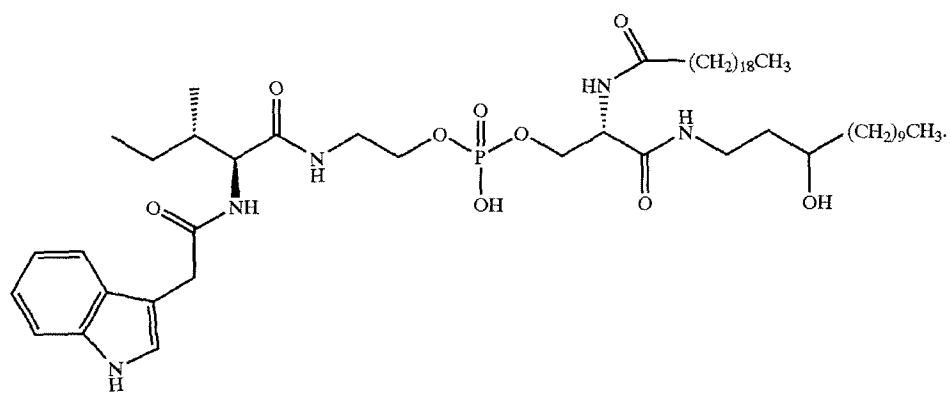
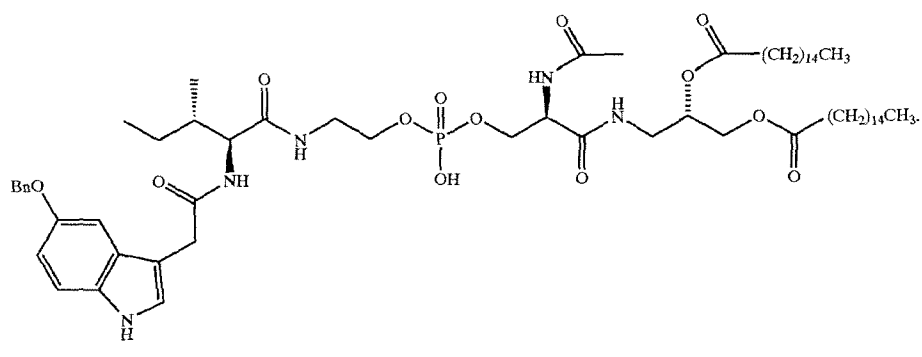
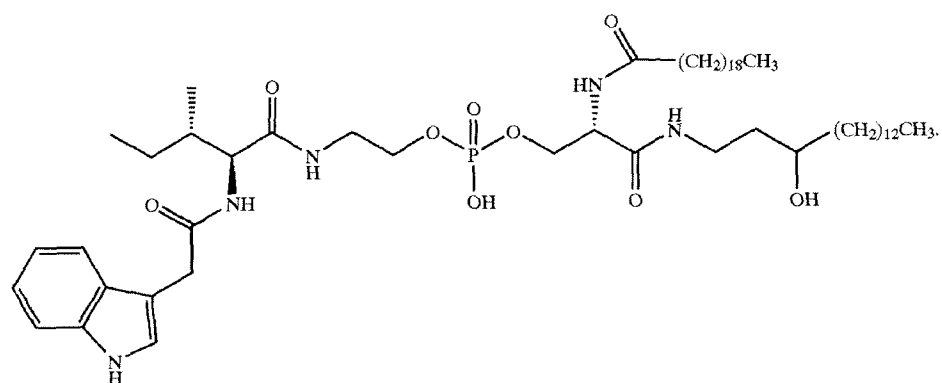
(VIII)

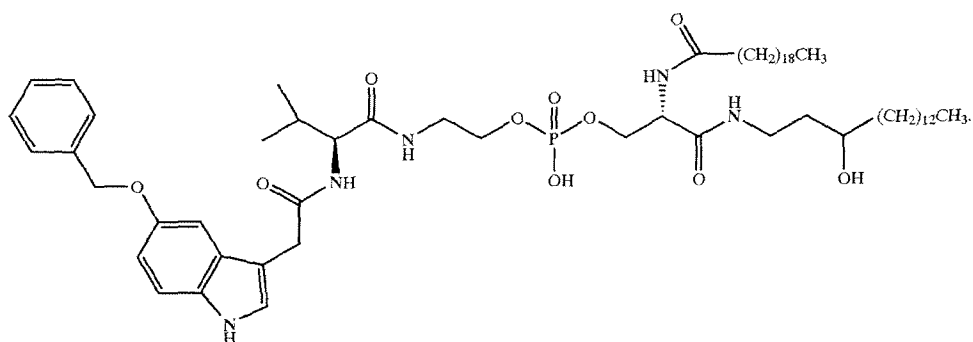
In still another aspect, a composition of the present invention comprises an antagonist to TLR2 receptor, as disclosed in US Patent Application Publication 2005/0113345, which is incorporated herein by reference. Non-limiting examples of such an antagonist include the following compounds.



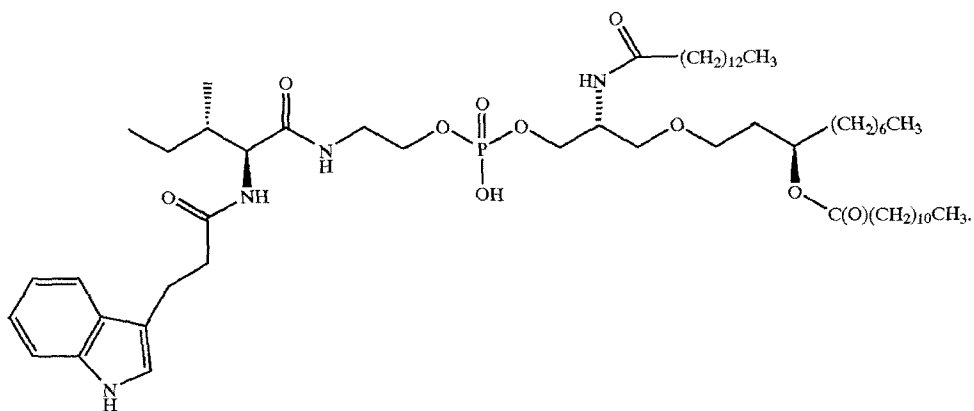
(IX)



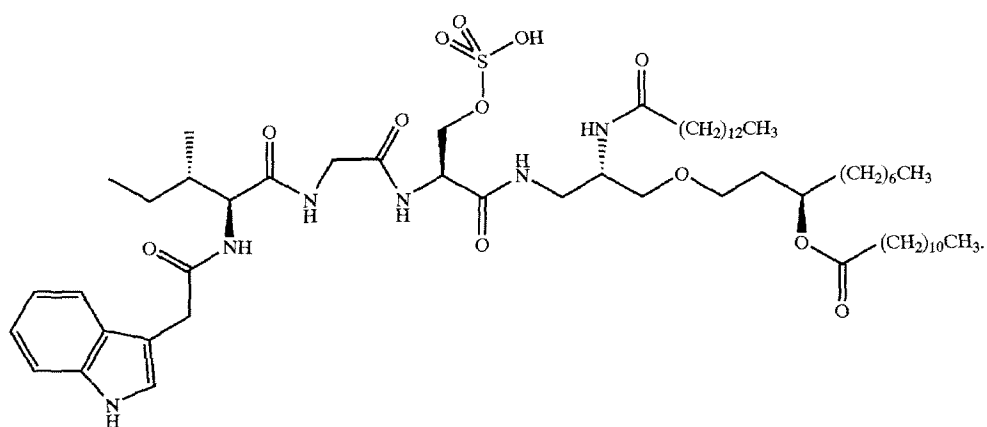




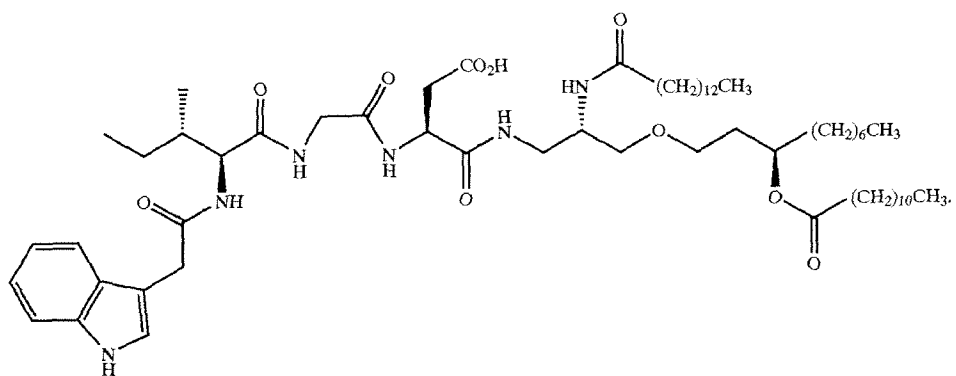
(XVIII)



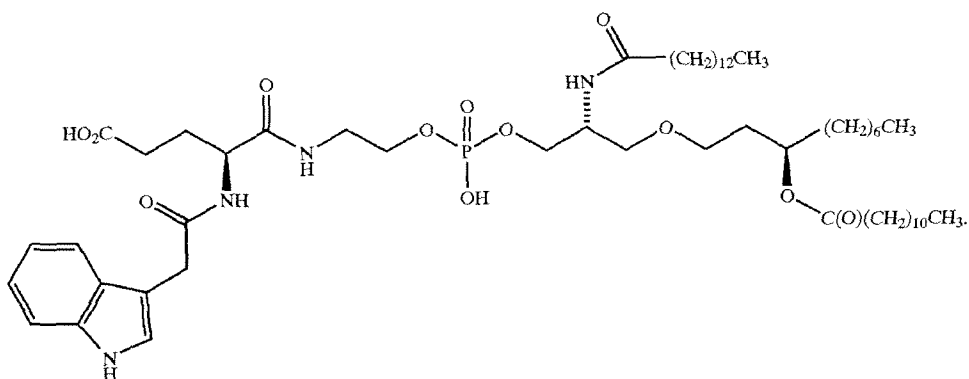
(XIX)



(XX)



(XXI)



(XXII)

In still another aspect, a composition of the present invention comprises an antibody that binds to and inhibits the activity of TLR4/MD2 complex in the production of inflammatory cytokines. Non-limiting examples of such antibodies comprise heavy chains comprising one of the following non-limiting examples of complementary determining regions ("CDRs"): DSYIH (SEQ. NO. 9); WTDPENVNSIYDPRFQG (SEQ. NO. 10); GYNGVYYAMDY (SEQ. NO. 11); DYWIE (SEQ. NO. 12); EILPGSGSTNYNEDFKD (SEQ. NO. 13); EERAYYFGY (SEQ. NO. 14); GGYSWH (SEQ. NO. 15); YIHYSGYTDFNPSLKT (SEQ. NO. 16); KDPSDGFY (SEQ. NO. 17); TYNIGVG (SEQ. NO. 18); HIWWNDNIYYNTVLKS (SEQ. NO. 19); and MAEGRYDAMDY (SEQ. NO. 20), as disclosed in US Patent Application Publication 2005/0265998, which is incorporated herein by reference. Such a CDR may comprise a combination of SEQ. No. 9 – SEQ. NO. 20.

In still another aspect, a composition of the present invention comprises an antibody that binds to and inhibits the activity of TLR4/CD14 complex in the production of inflammatory cytokines, as disclosed in US Patent Application Publication 2006/0257411, which is incorporated herein by reference.

In yet another aspect, an antagonist to a human TLR, an antagonist to a coreceptor of a human TLR, or a compound capable of inhibiting activation of a human TLR signaling pathway ("inhibitor of a TLR") is included in a composition of the present invention in an amount from about 0.0001 to about 10 percent by weight of the composition. Alternatively, such an antagonist or an inhibitor of a TLR is present in a composition of the present invention in an amount from about 0.001 to about 5 percent (from about 0.001 to about 2, or from about 0.001 to about 1, or from about 0.001 to

about 0.5, or from about 0.001 to about 0.2, or from about 0.001 to about 0.1, or from about 0.01 to about 0.1, or from about 0.01 to about 0.5, or from about 0.001 to about 0.01, or from about 0.001 to about 0.1 percent) by weight of the composition.

In another aspect, a composition of the present invention comprises: (a) a TLR antagonist or a TLR-coreceptor antagonist; and (b) an anti-inflammatory agent.

In one embodiment, such an anti-inflammatory agent is selected from the group consisting of non-steroidal anti-inflammatory drugs ("NSAIDs"), peroxisome proliferator-activated receptor ("PPAR") ligands, combinations thereof, and mixtures thereof.

Non-limiting examples of the NSAIDs are: aminoarylcarboxylic acid derivatives (e.g., enfenamic acid, etofenamate, flufenamic acid, isonixin, meclofenamic acid, mefenamic acid, niflumic acid, talniflumate, terofenamate, tolfenamic acid), arylacetic acid derivatives (e.g., aceclofenac, acemetacin, alclofenac, amfenac, amtolmetin guacil, bromfenac, bufexamac, cinmetacin, clopirac, diclofenac sodium, etodolac, felbinac, fenclozic acid, fentiazac, glucametacin, ibufenac, indomethacin, isofezolac, isoxepac, lonazolac, metiazinic acid, mofezolac, oxametacine, pirazolac, proglumetacin, sulindac, tiaramide, tolmetin, tropesin, zomepirac), arylbutyric acid derivatives (e.g., bumadizon, butibufen, fenbufen, xenbucin), arylcarboxylic acids (e.g., clidanac, ketorolac, tinoridine), arylpropionic acid derivatives (e.g., alminoprofen, benoxaprofen, bermoprofen, bucloxic acid, carprofen, fenoprofen, flunoxaprofen, flurbiprofen, ibuprofen, ibuproxam, indoprofen, ketoprofen, loxoprofen, naproxen, oxaprozin, piketoprolen, pirprofen, pranoprofen, protizinic acid, suprofen, tiaprofenic acid, ximoprofen, zaltoprofen), pyrazoles (e.g., difenamizole, epirizole), pyrazolones (e.g., apazone, benzpiperylon, feprazone, mofebutazone, morazone, oxyphenbutazone, phenylbutazone, pipebuzone, propyphenazone, ramifenazone, suxibuzone, thiazolinobutazone), salicylic acid derivatives (e.g., acetaminosalol, aspirin, benorylate, bromosaligenin, calcium acetylsalicylate, diflunisal, etersalate, fendosal, gentisic acid, glycol salicylate, imidazole salicylate, lysine acetylsalicylate, mesalamine, morpholine salicylate, 1-naphthyl salicylate, olsalazine, parsalimide, phenyl acetylsalicylate, phenyl salicylate, salacetamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalate, sulfasalazine), thiazinecarboxamides (e.g., ampiroxicam, droxicam, isoxicam,

lornoxicam, piroxicam, tenoxicam), ϵ -acetamidocaproic acid, S-(5'-adenosyl)-L-methionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, α -bisabolol, bucolome, difenpiramide, ditazol, emorfazone, fepradinol, guaiazulene, nabumetone, nimesulide, oxaceprol, paranyline, perisoxal, proquazone, superoxide dismutase, tenidap, zileuton, their physiologically acceptable salts, combinations thereof, and mixtures thereof.

In another aspect of the present invention, an anti-inflammatory agent is a PPAR-binding molecule. In one embodiment, such a PPAR-binding molecule is a PPAR α -, PPAR δ -, or PPAR γ -binding molecule. In another embodiment, such a PPAR-binding molecule is a PPAR α , PPAR δ , or PPAR γ agonist. Such a PPAR ligand binds to and activates PPAR to modulate the expression of genes containing the appropriate peroxisome proliferator response element in its promoter region.

PPAR γ agonists can inhibit the production of TNF- α and other inflammatory cytokines by human macrophages (C-Y. Jiang et al., *Nature*, Vol. 391, 82-86 (1998)) and T lymphocytes (A.E. Giorgini et al., *Horm. Metab. Res.* Vol. 31, 1-4 (1999)). More recently, the natural PPAR γ agonist 15-deoxy- Δ -12,14-prostaglandin J2 (or "15-deoxy- Δ -12,14-PG J2"), has been shown to inhibit neovascularization and angiogenesis (X. Xin et al., *J. Biol. Chem.* Vol. 274:9116-9121 (1999)) in the rat cornea. Spiegelman et al., in U.S. Patent 6,242,196, disclose methods for inhibiting proliferation of PPAR γ -responsive hyperproliferative cells by using PPAR γ agonists; numerous synthetic PPAR γ agonists are disclosed by Spiegelman et al., as well as methods for diagnosing PPAR γ -responsive hyperproliferative cells. All documents referred to herein are incorporated by reference. PPARs are differentially expressed in diseased versus normal cells. PPAR γ is expressed to different degrees in the various tissues of the eye, such as some layers of the retina and the cornea, the choriocapillaris, uveal tract, conjunctival epidermis, and intraocular muscles (see, e.g., U.S. Patent 6,316,465).

In one aspect, a PPAR γ agonist used in a composition or a method of the present invention is a thiazolidinedione, a derivative thereof, or an analog thereof. Non-limiting examples of thiazolidinedione-based PPAR γ agonists include pioglitazone, troglitazone, ciglitazone, englitazone, rosiglitazone, and chemical derivatives thereof. Other PPAR γ agonists include Clofibrate (ethyl 2-(4-chlorophenoxy)-2-

methylpropionate), clofibric acid (2-(4-chlorophenoxy)-2-methylpropanoic acid), GW 1929 (N-(2-benzoylphenyl)-O-{2-(methyl-2-pyridinylamino)ethyl}-L-tyrosine), GW 7647 (2-{4-{2-{{(cyclohexylamino)carbonyl}(4-cyclohexylbutyl)amino}ethyl}phenyl}thio}-2-methylpropanoic acid), and WY 14643 ({4-chloro-6-{{(2,3-dimethylphenyl)amino}-2-pyrimidinyl}thio}acetic acid). GW 1929, GW 7647, and WY 14643 are commercially available, for example, from Koma Biotechnology, Inc. (Seoul, Korea). In one embodiment, the PPAR γ agonist is 15-deoxy- Δ -12, 14-PG J2.

Non-limiting examples of PPAR- α agonists include the fibrates, such as fenofibrate and gemfibrozil. A non-limiting example of PPAR- δ agonist is GW501516 (available from Axxora LLC, San Diego, California or EMD Biosciences, Inc., San Diego, California).

Each of said anti-inflammatory agents, when included in a composition, is present in a composition of the present invention in an amount from about 0.001 to about 5 percent (or from about 0.001 to about 2, or from about 0.001 to about 1, or from about 0.001 to about 0.5, or from about 0.001 to about 0.2, or from about 0.001 to about 0.1, or from about 0.01 to about 0.1, or from about 0.01 to about 0.5, or from about 0.001 to about 0.01, or from about 0.001 to about 0.1 percent) by weight of the composition.

Other Suitable Ingredients in a Composition of the Present Invention

In addition to an antagonist to at least a human TLR, an antagonist to a coreceptor of a human TLR, or an inhibitor to a human TLR or a coreceptor thereof, a composition of the present invention comprises a liquid medium. In one embodiment, the liquid medium comprises an aqueous solution.

In another aspect, a composition of the present invention further comprises a material selected from the group consisting of preservatives, antimicrobial agents, surfactants, buffers, tonicity-modifying agents, chelating agents, viscosity-modifying agents, co-solvents, oils, humectants, emollients, stabilizers, antioxidants and combinations thereof.

Water-soluble preservatives that may be employed in a composition of the present invention include benzalkonium chloride, benzoic acid, benzoyl chloride, benzyl alcohol, chlorobutanol, calcium ascorbate, ethyl alcohol, potassium sulfite, sodium ascorbate, sodium benzoate, sodium bisulfite, sodium bisulfate, sodium thiosulfate, thimerosal, methylparaben, ethylparaben, propylparaben, polyvinyl alcohol, phenylethyl alcohol, quaternary alkyl ammonium salts (such as Polyquaternium-1 or Polyquaternium-10), hydrogen peroxide, and urea peroxide, and biguanides. Other preservatives useful in the present invention include, but are not limited to, the FDA-approved preservative systems for food, cosmetics, and pharmaceutical preparations. These agents may be present in individual amounts of from about 0.001 to about 5 percent by weight (preferably, from about 0.01 percent to about 2 percent by weight; more preferably, from about 0.01 percent to about 1 percent by weight).

In one embodiment, a composition of the present invention comprises an antimicrobial agent. Non-limiting examples of antimicrobial agents include the quaternary ammonium compounds and bisbiguanides. Representative examples of quaternary ammonium compounds include benzalkonium halides and balanced mixtures of n-alkyl dimethyl benzyl ammonium chlorides. Other examples of antimicrobial agents include polymeric quaternary ammonium salts used in ophthalmic applications such as poly[(dimethyliminio)-2-butene-1,4-diyl chloride], [4-tris(2-hydroxyethyl)ammonio]-2-butenyl-w-[tris(2-hydroxyethyl)ammonio]dichloride (chemical registry number 75345-27-6) generally available as Polyquaternium-1[®] from ONYX Corporation.

Non-limiting examples of antimicrobial biguanides include the bis(biguanides), such as alexidine or chlorhexidine or salts thereof, and polymeric biguanides such as polymeric hexamethylene biguanides ("PHMB") and their water-soluble salts, which are available, for example, from Zeneca, Wilmington, Delaware.

In one aspect, a composition of the present invention includes a disinfecting amount of an antimicrobial agent that will at least prevent the growth of microorganisms in the formulations employed. Preferably, a disinfecting amount is that which will reduce the microbial burden by two log orders in four hours and more preferably by one log order in one hour. Typically, such agents are present in concentrations ranging from about 0.00001 to about 0.5 percent (w/v); preferably, from about 0.00003 to about 0.5

percent (w/v); and more preferably, from about 0.0003 to about 0.1 percent (w/v).

In another aspect, a composition of the present invention comprises a surfactant. Suitable surfactants can be amphoteric, cationic, anionic, or non-ionic, which may be present (individually or in combination) in amounts up to 15 percent, preferably up to 5 percent weight by volume (w/v) of the total composition (solution). In one embodiment, the surfactant is an amphoteric or non-ionic surfactant, which when used imparts cleaning and conditioning properties. The surfactant should be soluble in the lens care solution and non-irritating to eye tissues. Many non-ionic surfactants comprise one or more chains or polymeric components having oxyalkylene ($-O-R-$) repeating units wherein R has 2 to 6 carbon atoms. Preferred non-ionic surfactants comprise block polymers of two or more different kinds of oxyalkylene repeat units. Satisfactory non-ionic surfactants include polyethylene glycol esters of fatty acids, polysorbates, polyoxyethylene, or polyoxypropylene ethers of higher alkanes (C_{12} - C_{18}). Non-limiting examples of the preferred class include polysorbate 80 (polyoxyethylene sorbitan monooleate), polysorbate 60 (polyoxyethylene sorbitan monostearate), polysorbate 20 (polyoxyethylene sorbitan monolaurate), commonly known by their trade names of Tween® 80, Tween® 60, Tween® 20), poloxamers (synthetic block polymers of ethylene oxide and propylene oxide, such as those commonly known by their trade names of Pluronic®; e.g., Pluronic® F127 or Pluronic® F108), or poloxamines (synthetic block polymers of ethylene oxide and propylene oxide attached to ethylene diamine, such as those commonly known by their trade names of Tetronic®; e.g., Tetronic® 1508 or Tetronic® 908, etc., other nonionic surfactants such as Brij®, Myrj®, and long chain fatty alcohols (i.e., oleyl alcohol, stearyl alcohol, myristyl alcohol, docosohexanoyl alcohol, etc.) with carbon chains having about 12 or more carbon atoms (e.g., such as from about 12 to about 24 carbon atoms). Such compounds are delineated in Martindale, 34th ed., pp 1411-1416 (Martindale, "The Complete Drug Reference," S. C. Sweetman (Ed.), Pharmaceutical Press, London, 2005) and in Remington, "The Science and Practice of Pharmacy," 21st Ed., p. 291 and the contents of chapter 22, Lippincott Williams & Wilkins, New York, 2006). The concentration of a non-ionic surfactant, when present, in a composition of the present invention can be in the range from about 0.001 to about 5 weight percent (or alternatively, from about 0.01 to about 4, or from about 0.01 to about 2, or from about 0.01 to about 1 weight percent).

Various other ionic as well as amphoteric and anionic surfactants suitable for use in the invention can be readily ascertained, in view of the foregoing description, from McCutcheon's Detergents and Emulsifiers, North American Edition, McCutcheon Division, MC Publishing Co., Glen Rock, N.J. 07452 and the CTFA International Cosmetic Ingredient Handbook, Published by The Cosmetic, Toiletry, and Fragrance Association, Washington, D.C.

Amphoteric surfactants suitable for use in a composition according to the present invention include materials of the type offered commercially under the trade name "Miranol." Another useful class of amphoteric surfactants is exemplified by cocoamidopropyl betaine, commercially available from various sources.

The foregoing surfactants will generally be present in a total amount from 0.001 to 5 percent weight by volume (w/v), or 0.01 to 5 percent, or 0.01 to 2 percent, or 0.1 to 1.5 percent (w/v).

In another aspect, the pH of a composition of the present invention is maintained within the range of 5 to 8, preferably about 6 to 8, more preferably about 6.5 to 7.8. Non-limiting examples of suitable buffers include boric acid, sodium borate, potassium citrate, citric acid, sodium bicarbonate, TRIS, and various mixed phosphate buffers (including combinations of Na_2HPO_4 , NaH_2PO_4 and KH_2PO_4) and mixtures thereof. Borate buffers are preferred, particularly for enhancing the efficacy of biguanides, when they are used in compositions of the present invention. Generally, buffers will be used in amounts ranging from about 0.05 to 2.5 percent by weight, and preferably, from 0.1 to 1.5 percent. In certain embodiments of this invention, the compositions comprise a borate or mixed phosphate buffer, containing one or more of boric acid, sodium borate, potassium tetraborate, potassium metaborate, or mixtures of the same.

In addition to buffering agents, in some instances it may be desirable to include chelating or sequestering agents in the present compositions in order to bind metal ions, which might otherwise react with the lens and/or protein deposits and collect on the lens. Ethylene-diaminetetraacetic acid ("EDTA") and its salts (disodium) are preferred examples. They are usually added in amounts ranging from about 0.01 to about

0.3 weight percent. Other suitable sequestering agents include phosphonic acids, gluconic acid, citric acid, tartaric acid, and their salts; e.g., sodium salts.

In another aspect, compositions of the present invention comprise a tonicity-adjusting agent, to approximate the osmotic pressure of normal lacrimal fluid, which is equivalent to a 0.9 percent solution of sodium chloride or 2.5 percent of glycerol solution. Non-limiting examples of suitable tonicity-adjusting agents include, but are not limited to, sodium and potassium chloride, calcium and magnesium chloride, dextrose, glycerin, mannitol, and sorbitol. These agents are typically used individually in amounts ranging from about 0.01 to 2.5 percent (w/v) and preferably, from about 0.2 to about 1.5 percent (w/v). Preferably, the tonicity-adjusting agent will be employed in an amount to provide a final osmotic value of 200 to 450 mOsm/kg; more preferably, between about 250 to about 350 mOsm/kg, and most preferably between about 280 to about 320 mOsm/Kg.

In another aspect, it may be desirable to include one or more water-soluble viscosity-modifying agents in the compositions of the present invention. Because of their demulcent effect, viscosity-modifying agents have a tendency to enhance the patient's comfort by means of a lubricating film on the eye. Included among the water-soluble viscosity-modifying agents are the cellulose polymers like hydroxyethyl or hydroxypropyl cellulose, carboxymethyl cellulose and the like. Such viscosity-modifying agents may be employed in amounts ranging from about 0.01 to about 4 weight percent or less. The present compositions may also include optional demulcents.

In addition, a composition of the present invention can include additives such as co-solvents, oils, humectants, emollients, stabilizers, or antioxidants for a variety of purposes. These additives may be present in amounts sufficient to provide the desired effects, without impacting the performance of other ingredients.

DEMONSTRATION OF INHIBITION OF PRODUCTION OF PRO-INFLAMMATORY CHEMOKINES

EXPERIMENT 1: Inhibitory ODN suppression of neutrophils activated by synthetic stimulatory ODN sequence, bacterial DNA, and whole bacteria, but not by specific TLR ligand Pam3Cys or LPS.

In one experiment, mouse peritoneal neutrophils were isolated from C57BL/6 mice that had received intraperitoneal injection of 1% casein solution containing 0.5mM MgCl₂ and 0.99mM CaCl₂ 16 hours and 3 hours prior to harvesting in Hank's balanced salt solution ("HBSS") lavage. Collected cells were centrifuged (2000 rpm, 10 minutes) and washed twice in HBSS, prior to separation of granulocytes by Percol gradient at 31,500 rpm for 20 min. Cells were washed twice and resuspended in Dubelco's modified eagle's medium ("DMEM") containing 10% fetal calf serum (Invitrogen, Basel Switzerland). Purity of 98% neutrophils was verified by Diff-Quik stain (VWR, Bridgeport, NJ). Neutrophils (1X10⁵ /well) were pre-incubated with 100ng/ml GM-CSF at 37°C for 1 hour prior to exposure to compositions of the present invention comprising 0.08 – 10 µg/ml of inhibitory ODN 2088 (InvivoGen, San Diego, CA; sequence disclosed above) or a control composition containing 20 µg/ml of the control ODN 1911 (Operon Qiagen, Valencia, California; having a sequence of TCCAGGACTTTCCTCAGGTT), or the medium only, for 30 minutes prior to activation with 20 µg/ml of stimulatory ODN 1826 (Operon Qiagen, Valencia, California; having a sequence of TCCATGACGTTTCCTGACGTT); 20 µg/ml of endotoxin-free DNA from *E. coli* K12 (InvivoGen, San Diego, CA); killed *Staphylococcus aureus* strain E2061740 (3x10⁵ cfu/ml); 100 ng/ml of Pam3Cys (synthetic lipopeptide (S)-(2,3-bis(palmitoyloxy)-(2RS)-propyl)-N-palmitoyl-(R)-Cys-(S)-Ser-(S)-Lys₄-OH, EMC Microcollections, Tubingen, Germany); or 200 ng/ml of LPS (ultra pure lipopolysaccharide from *E. coli* 0111:B4 strain, InvivoGen, San Diego, California). After 15 hours at 37°C, supernates were collected for ELISA assay (R&D Systems, Minneapolis, MN) for pro-inflammatory cytokines macrophage inflammatory protein-2 ("MIP-2"), keratinocyte-derived chemokines ("KC"), IL-6, and TNF-α. Results of cytokine concentrations are shown in Figures 1-4. The composition containing the inhibitory ODN 2088 inhibited pro-inflammatory cytokine production by neutrophils upon exposure to the synthetic stimulatory ODN 1826 or bacterial DNA in a dose dependent manner. Furthermore, the composition containing the inhibitory ODN 2088 prevented the production of pro-inflammatory cytokines, as exhibited by the nondetectable levels of these four cytokines, when neutrophils were activated with killed *Staphylococcus aureus*. The production of these pro-inflammatory cytokines was not affected when neutrophils activated by Pam3Cys or LPS were treated with a composition comprising the inhibitory ODN 2088. This not surprising in view of the fact that the inhibitory ODN 2088 inhibits the activation

of TLR9 while LPS and Pam3Cys activate TLR4 and TLR2, respectively. Other inhibitors of TLR2 and TLR4 activation should be effective in suppressing corneal infiltrate induced by LPS and Pam3Cys, respectively.

EXPERIMENT 2-1: Inhibitory ODN suppression of mouse keratitis induced by synthetic stimulatory ODN sequence or bacterial DNA, but not by TLR ligand Pam3Cys or LPS.

In this experiment, 1 μ l of test solution containing 20 μ g/ml of the synthetic stimulatory ODN 1826, 10 μ g/ml of endotoxin-free DNA from *E. coli* K12, 20 μ g/ml of Pam3Cys, or 20 μ g/ml LPS, along with a composition of the present invention containing the inhibitory ODN 2088, the control composition containing 20 μ g/ml of ODN 1911, or medium only, was applied to a 1 mm² abraded area of central C57BL/6 mouse cornea that had been marked by sterile trephine (Miltex, Tuttlingen, Germany) and abraded with an Alger brush II (Alger, PagoVista, Texas). After 24 hours, the corneal infiltrate was determined as the number of neutrophils per corneal section. The results are shown in Figure 5. The inhibitory ODN 2088 reduced the number of infiltrating neutrophils in response to the stimulatory ODN 1826 or bacterial DNA. The inhibitory ODN 2088 was not effective in suppressing corneal infiltrates in response to Pam3Cys or LPS activation because ODN 2088 inhibits TLR 9 activation while LPS and Pame3Cys activate TLR2 and TLR4, respectively. Other inhibitors of TLR2 and TLR4 activation should be effective in suppressing corneal infiltrate induced by Pam3Cys and LPS, respectively.

EXPERIMENT 2-2: Inhibitory ODN suppression of mouse pro-inflammatory cytokines induced by stimulatory ODN.

In this experiment, 1 μ l of test solution containing 20 μ g/ml of the synthetic stimulatory ODN 1826, along with a composition of the present invention containing 20 μ g/ml of the inhibitory ODN 2088, or a control composition containing 20 μ g/ml of the control ODN 1911, or the medium only, was applied to a 1 mm² abraded area of central C57BL/6 mouse cornea that had been marked by sterile trephine (Miltex, Tuttlingen, Germany) and abraded with an Alger brush II (Alger, PagoVista, TX). After 5 hours, the corneal epithelium was separated after 20 minutes in 20mM EDTA at 37°C and placed into RPMI 1640 medium. Samples were disrupted by sonication for 88 seconds with 40% duty cycle (Vibracell; Sonics and Material, Danbury, Connecticut). Cytokines were

measured by ELISA assay (R&D Systems, Minneapolis, MN) for the pro-inflammatory cytokines MIP-2, KC, and human interferon-inducible protein 10 ("IP-10"). The results are shown in Figure 6. The inhibitory ODN 2088 reduced cytokine response to the stimulatory ODN 1826 for all three cytokines measured.

EXPERIMENT 3: Inhibitory ODN and vitamin D suppression of TLR ligand activation of human cell lines.

Three human cell lines representative of immune responsive cells of the ocular surface (HCEL, a human corneal epithelial cell line representative of cells present on the ocular surface; HL-60, a neutrophil-like cell line representative of neutrophils present in the tear layer, especially in the closed eye; and U937, a macrophage cell line representative of dendritic cells of the cornea, especially of those at the limbus) were exposed to various concentrations of compositions of the present invention containing the inhibitory ODN TTAGGG (InvivoGen, San Diego, CA) and vitamin D (1 α ,25-Dihydroxyvitamin D₃, Sigma-Aldrich, St. Louis, Missouri) and control compositions containing prednisolone (1,4-Pregnadiene-11 β ,17 α ,21-triol-3,20-dione, Sigma-Aldrich, St. Louis, Missouri) for 1 hour prior to activation by the TLR ligand Pam3Cys for 6 hour, flagellin (flagellin purified from *Salmonella typhimurium*, InvivoGen, San Diego, California) for 24 hr, or the stimulatory CpG type B ODN 2006 (Invivogen, San Diego, California) for 24 hours. After incubation at 37°C, supernates were collected for ELISA assay (R&D Systems, Minneapolis, Minnesota) for the pro-inflammatory cytokine CXCL8 ("IL-8"). Results of cytokine concentrations are shown in Figure 7. Both the inhibitory ODN TTAGGG and vitamin D inhibited cytokine response to TLR ligand activation of each cell line in an inhibitor-specific manner. The inhibitory ODN TTTAGGG reduced the cytokine response of each cell type to Pam3Cys, and of the U937 cell line to the stimulatory CpGB ODN 2006 activation. Vitamin D reduced the cytokine response to Pam3Cys activation of HCEL line and the flagellin activation of HL-60 and U937 lines. Prednisolone inhibited Pam3Cys and flagellin activation of each cell line, except Pam3Cys activation of U937 cell line. Inhibition of the stimulatory ODN CpGB ODN 2006 was only tested with inhibitory ODN TTAGGG on U937 cells.

Thus, the foregoing experiments demonstrate that TLR antagonists can inhibit the production of various pro-inflammatory cytokines, and therefore, can prevent or

control their damaging effects on ocular tissues. It is expected that such inhibition can be effective in providing ocular neuroprotection.

The following examples serve to illustrate some non-limiting compositions of the present invention. The ingredients shown in each of Tables 1-10 are mixed to form a pharmaceutical composition for treating or controlling ocular neurodegenerative conditions.

EXAMPLE 1:

Table 1

Ingredient	Amount (percent w/v)
Polyhexamethylenebiguanide HCl (as a 20 percent w/w solution available under the mark Cosmocil CQ, from ICI Chemical Co.)	0.00047
Boric acid	0.64
Sodium borate	0.12
Edetate disodium	0.11
Sodium chloride	0.49
Poloxamine (Tetronic® 1107 from BASF)	1.00
Tetrasodium etidronate (as a 30 percent w/w solution, available under the mark DeQuest® 2016 from Monsanto Co.)	0.01
ODN 2088	0.005
Hydrochloric acid (1N) or sodium hydroxide (1N)	as required to adjust pH to 7-7.5
Purified water	q.s. to 100

EXAMPLE 2:

Table 2

Ingredient	Amount (percent w/v)
Polyhexamethylenebiguanide HCl (as a 20 percent w/w solution available under the mark Cosmocil CQ, from ICI Chemical Co.)	0.00047
Boric acid	0.64
Sodium borate	0.12
Edetate disodium	0.11
Sodium chloride	0.49
Polysorbate 80	0.7
ODN 2088	0.01
Hydrochloric acid (1N) or sodium hydroxide (1N)	as required to adjust pH to 7-7.5
Purified water	q.s. to 100

EXAMPLE 3:

Table 3

Ingredient	Amount (percent w/v)
Polyhexamethylenebiguanide HCl (as a 20 percent w/w solution available under the mark Cosmocil CQ, from ICI Chemical Co.)	0.0006
Phosphate buffer	0.5
Edetate disodium	0.11
Sodium chloride	0.49
Polysorbate 80	0.7
Tetrasodium etidronate (as a 30 percent w/w solution, available under the mark DeQuest® 2016 from Monsanto Co.)	0.01
Vitamin D ₃	0.2
Purified water	q.s. to 100

EXAMPLE 4:

Table 4

Ingredient	Amount (percent w/v)
Polyhexamethylenebiguanide HCl (as a 20 percent w/w solution available under the mark Cosmocil CQ, from ICI Chemical Co.)	0.0005
Boric acid	0.64
Sodium borate	0.12
Edetate disodium	0.11
Sodium chloride	0.49
Polysorbate 80	0.7
Purified anti-human TLR2 antibody (for example from eBioscience, San Diego, California)	0.03
Hydrochloric acid (1N) or sodium hydroxide (1N)	as required to adjust pH to 7-7.5
Purified water	q.s. to 100

EXAMPLE 5:

Table 5

Ingredient	Amount (percent w/v)
Polyhexamethylenebiguanide HCl (as a 20 percent w/w solution available under the mark Cosmocil CQ, from ICI Chemical Co.)	0.0005
Boric acid	0.64
Sodium borate	0.12
Edetate disodium	0.11
Sodium chloride	0.49
Polysorbate 80	0.7
Tetrasodium etidronate (as a 30 percent w/w solution, available under the mark DeQuest® 2016 from Monsanto Co.)	0.01
Soluble TLR4 consisting of the putative extracellular domain (Met ¹ -Lys ⁶³¹ , see H. Mitsuzawa et al., <i>J. Immunol.</i> , Vol. 177, 8133 (2006) and N. Hyakushima et al., <i>J. Immunol.</i> , Vol. 173, 6949 (2004))	0.02
Hydrochloric acid (1N) or sodium hydroxide (1N)	as required to adjust pH to 7-7.5
Purified water	q.s. to 100

EXAMPLE 6:

Table 6

Ingredient	Amount (percent w/v)
Polyhexamethylenebiguanide HCl (as a 20 percent w/w solution available under the mark Cosmocil CQ, from ICI Chemical Co.)	0.00047
Boric acid	0.64
Sodium borate	0.12
Edetate disodium	0.11
Sodium chloride	0.49
Polysorbate 80	0.7
Tetrasodium etidronate (as a 30 percent w/w solution, available under the mark DeQuest® 2016 from Monsanto Co.)	0.01
Chloroquine	0.001
ODN 2088	0.01
Hydrochloric acid (1N) or sodium hydroxide (1N)	as required to adjust pH to 7-7.5
Purified water	q.s. to 100

EXAMPLE 7:

Table 7

Ingredient	Amount (percent w/v)
Polyhexamethylenebiguanide HCl (as a 20 percent w/w solution available under the mark Cosmocil CQ, from ICI Chemical Co.)	0.0005
Boric acid	0.64
Sodium borate	0.12
Edetate disodium	0.11
Sodium chloride	0.49
Polysorbate 80	0.7
Recombinant soluble MD-2 (see H. Mitsuzawa et al., <i>J. Immunol.</i> , Vol. 177, 8133 (2006) and N. Hyakushima et al., <i>J. Immunol.</i> , Vol. 173, 6949 (2004))	0.02
Hydrochloric acid (1N) or sodium hydroxide (1N)	as required to adjust pH to 7-7.5
Purified water	q.s. to 100

EXAMPLE 8:

Table 8

Ingredient	Amount (percent w/v)
Polyhexamethylenebiguanide HCl (as a 20 percent w/w solution available under the mark Cosmocil CQ, from ICI Chemical Co.)	0.0005
Boric acid	0.64
Sodium borate	0.12
Edetate disodium	0.11
Sodium chloride	0.49
Polysorbate 80	0.7
Tetrasodium etidronate (as a 30 percent w/w solution, available under the mark DeQuest® 2016 from Monsanto Co.)	0.01
Purified anti-human TLR2 antibody (for example from eBioscience, San Diego, California)	0.01
Purified anti-human TLR3 antibody (for example from eBioscience, San Diego, California)	0.01
Purified anti-human TLR4 antibody (for example from eBioscience, San Diego, California)	0.01
Hydrochloric acid (1N) or sodium hydroxide (1N)	as required to adjust pH to 7-7.5
Purified water	q.s. to 100

EXAMPLE 9:

Table 9

Ingredient	Amount (percent w/v)
Urea peroxide	0.06
Boric acid	0.64
Sodium borate	0.12
Edetate disodium	0.11
Sodium chloride	0.49
Polysorbate 80	0.7
Tetrasodium etidronate (as a 30 percent w/w solution, available under the mark DeQuest® 2016 from Monsanto Co.)	0.01
Purified anti-human TLR2 antibody (for example from eBioscience, San Diego, California)	0.01
Purified anti-human TLR3 antibody (for example from eBioscience, San Diego, California)	0.01
Purified anti-human TLR4 antibody (for example, from eBioscience, San Diego, California)	0.01
ODN 2088	0.01
Hydrochloric acid (1N) or sodium hydroxide (1N)	as required to adjust pH to 7-7.5
Purified water	q.s. to 100

EXAMPLE 10:

Table 10

Ingredient	Amount (percent w/v)
Polyquaternium-1	0.005
Boric acid	0.64
Sodium borate	0.12
Edetate disodium	0.11
Sodium chloride	0.49
Poloxamine (Tetronic® 1107 from BASF)	1.00
ODN having SEQ. NO. 24	0.05
Cyclosporine	0.05
Hydrochloric acid (1N) or sodium hydroxide (1N)	as required to adjust pH to 7-7.5
Purified water	q.s. to 100

In another aspect, a preservative other than polyhexamethylenebiguanide HCl may be used in any one of the foregoing formulation, in a suitably effective amount.

In still another aspect, a composition can be free of preservative if it is formulated to be used as a unit-dose composition. In such a case, the composition is packaged in an individual container that is opened and the contents of the container are used only once.

The present invention also provides a method for treating or controlling degeneration of at least a component of the optic nerve system. The method comprises applying a composition to the eye, wherein the composition comprises an antagonist to at least one human TLR, an antagonist to a coreceptor of a human TLR, or a compound that is capable of inhibiting an activation of a human TLR signaling pathway, or a combination thereof, in an effective amount for treating or controlling such degeneration.

In one aspect, an antagonist to at least one human TLR, an antagonist to a coreceptor of a human TLR, or a compound that is capable of inhibiting an activation of a human TLR signaling pathway, or a combination thereof is incorporated into a formulation for topical administration, systemic administration, periocular injection, or intravitreal injection. A formulation can desirably comprise a carrier that provides a sustained release of the active ingredients, such as for a period longer than about 1 week (or longer than about 1, 2, 3, 4, 5, or 6 months). In certain embodiments, the sustained-release formulation desirably comprises a carrier that is insoluble or only sparingly soluble in the ocular environment. Such a carrier can be an oil-based liquid, emulsion, gel, or semisolid. Non-limiting examples of oil-based liquids include castor oil, peanut oil, olive oil, coconut oil, sesame oil, cottonseed oil, corn oil, sunflower oil, fish-liver oil, arachis oil, and liquid paraffin.

In one embodiment, a composition of the present invention can be injected intravitreally to control the progression of an ocular neurodegenerative disease, using a fine-gauge needle, such as 25-33 gauge. Typically, an amount from about 25 μ l to about 100 μ l of a composition comprising an antagonist to at least one human TLR, an antagonist to a coreceptor of a human TLR, or a compound that is capable of inhibiting an activation of a human TLR signaling pathway, or a combination thereof is administered into a patient. A concentration of such an antagonist to at least one human TLR, an antagonist to a coreceptor of a human TLR, or a compound that is capable of inhibiting an activation of a human TLR signaling pathway, or a combination thereof is selected from the ranges disclosed above.

In another aspect, an antagonist to at least one human TLR, an antagonist to a coreceptor of a human TLR, or a compound that is capable of inhibiting an activation of a human TLR signaling pathway, or a combination thereof is incorporated into an ophthalmic device or system that comprises a biodegradable material, and the device is implanted into the posterior cavity of a diseased eye to provide a long-term (e.g., longer than about 1 week, or longer than about 1, 2, 3, 4, 5, or 6 months) control of progression of an ocular neurodegenerative disease. In one aspect, such control is achieved by reducing the levels of pro-inflammatory cytokines in tissues of the retina or optic nerve system over a long period of time.

In still another aspect, a method for controlling progression of an ocular degenerative disease comprises: (a) providing a composition comprising an antagonist to at least one human TLR, an antagonist to a coreceptor of a human TLR, a compound that is capable of inhibiting an activation of a human TLR signaling pathway, or a combination thereof; and (b) administering to a subject an effective amount of the composition at a frequency sufficient to control the progression of the ocular degenerative disease.

In one embodiment, an antagonist to at least one human TLR, an antagonist to a coreceptor of a human TLR, a compound that is capable of inhibiting an activation of a human TLR signaling pathway, or a combination thereof is selected from among those disclosed above.

In still another embodiment, the present invention provides a method for controlling progression of optic nerve degeneration in a subject having hypertensive glaucoma. The method comprises: (a) administering a composition comprising an antagonist to at least one human TLR, an antagonist to a coreceptor of a human TLR, a compound that is capable of inhibiting an activation of a human TLR signaling pathway, or a combination thereof to an eye of said subject; and (b) administering to the subject an intraocular-pressure ("IOP") lowering drug, wherein the composition and the IOP lowering drug are administered in effective amounts at a frequency sufficient to control the progression of optic nerve degeneration. Non-limiting examples of IOP lowering drugs include prostaglandin analogs (latanoprost, travoprost, bimatoprost), β -receptor antagonists (timolol maleate), α_2 -adrenergic agonists (brimonidine, clonidine), carbonic anhydrases (dorzolamide, brinzolamide), cholinomimetics (pilocarpine, carbachol), and inhibitors of acetylcholinesterase such as Echothiophate (phospholine iodide).

In preferred embodiment, a composition of the present invention is administered intravitreally. In still another aspect, a composition of the present invention is incorporated into an ophthalmic implant system or device, and the implant system or device is surgically implanted in the vitreous cavity of the patient for the sustained or long-term release of the active ingredient or ingredients. A typical implant system or device suitable for use in a method of the present invention comprises a biodegradable matrix with the active ingredient or ingredients impregnated or dispersed therein. Non-

limiting examples of ophthalmic implant systems or devices for the sustained-release of an active ingredient are disclosed in U.S. Patents 5,378,475; 5,773,019; 5,902,598; 6,001,386; 6,051,576; and 6,726,918; which are incorporated herein by reference.

In yet another aspect, a composition of the present invention is injected into the vitreous once a month, or once every two, three, four, five, or six months. In another aspect, the composition is implanted in the patient and is replaced at a frequency of, for example, once a year or at a suitable frequency that is determined to be appropriate for controlling the progression of the ocular degenerative disease.

COMBINATION THERAPY

A composition or a method of the present invention can be used in conjunction with other therapeutic, adjuvant, or prophylactic agents or methods commonly used to control (a) an increase of intraocular pressure, (b) a loss of neuronal cells of the retinal layers (such as retinal ganglion cells, Müller cells, amacrine cells, bipolar cells, horizontal cells, and photoreceptors) or (c) both, thus providing an enhanced overall treatment or enhancing the effects of the other therapeutic, prophylactic, or adjunctive agents or methods used to treat and manage the different ocular neurodegenerative diseases.

High doses may be required for some currently used therapeutic agents, or high frequency for currently used methods, to achieve levels to effectuate the target response, but may often be associated with a greater frequency of adverse effects. Thus, combined use of a composition of the present invention, with agents or methods commonly used to control progression of ocular nerve damage allows the use of relatively lower doses of such other agents, or frequency of such other methods, resulting in a lower frequency of potential adverse side effects associated with long-term administration of such therapeutic agents or methods. Thus, another indication of the compositions in this invention is to reduce adverse side effects of prior-art drugs or methods used to control optic nerve degeneration, such as the development of cataracts with long-acting anticholinesterase agents including demecarium, echothiophate, and isofluorophate.

In still another aspect, the present invention provides a method for preparing a composition for the treatment or control of an ocular neurodegenerative condition in a subject, which has an etiology in inflammation. The method comprises combining at least an antagonist to one human TLR, an antagonist to a coreceptor of a human TLR, or a compound that is capable of inhibiting an activation of a human TLR signaling pathway with a pharmaceutically acceptable carrier, diluent, excipient, additive, or combination thereof.

In one embodiment, a composition of the present invention is prepared to have a form of an emulsion, suspension, or dispersion. In another embodiment, the suspension or dispersion is based on an aqueous solution. For example, a composition of the present invention can comprise sterile saline solution.

A composition of the present invention can avoid one or more of the side effects of glucocorticoid therapy.

Glucocorticoids ("GCs") are among the most potent drugs used for the treatment of allergic and chronic inflammatory diseases. However, as mentioned above, long-term treatment with GCs is often associated with numerous adverse side effects, such as diabetes, osteoporosis, hypertension, glaucoma, or cataract. These side effects, like other physiological manifestations, are results of aberrant expression of genes responsible for such diseases. Research in the last decade has provided important insights into the molecular basis of GC-mediated actions on the expression of GC-responsive genes. GCs exert most of their genomic effects by binding to the cytoplasmic GC receptor ("GR"). The binding of GC to GR induces the translocation of the GC-GR complex to the cell nucleus where it modulates gene transcription either by a positive (transactivation) or negative (transrepression) mode of regulation. There has been growing evidence that both beneficial and undesirable effects of GC treatment are the results of undifferentiated levels of expression of these two mechanisms; in other words, they proceed at similar levels of effectiveness. Although it has not yet been possible to ascertain the most critical aspects of action of GCs in chronic inflammatory diseases, there has been evidence that it is likely that the inhibitory effects of GCs on cytokine synthesis are of particular importance. GCs inhibit the transcription, through the transrepression mechanism, of several cytokines that are relevant in inflammatory

diseases, including IL-1 β (interleukin-1 β), IL-2, IL-3, IL-6, IL-11, TNF- α (tumor necrosis factor- α), GM-CSF (granulocyte-macrophage colony-stimulating factor), and chemokines that attract inflammatory cells to the site of inflammation, including IL-8, RANTES, MCP-1 (monocyte chemotactic protein-1), MCP-3, MCP-4, MIP-1 α (macrophage-inflammatory protein-1 α), and eotaxin. P.J. Barnes, *Clin. Sci., Vol.*, Vol. 94, 557-572 (1998). On the other hand, there is persuasive evidence that the synthesis of I κ B kinases, which are proteins having inhibitory effects on the NF- κ B pro-inflammatory transcription factors, is increased by GCs. These pro-inflammatory transcription factors regulate the expression of genes that code for many inflammatory proteins, such as cytokines, inflammatory enzymes, adhesion molecules, and inflammatory receptors. S. Wissink et al., *Mol. Endocrinol.*, Vol. 12, No. 3, 354-363 (1998); P.J. Barnes and M. Karin, *New Engl. J. Med.*, Vol. 336, 1066-1077 (1997). Thus, both the transrepression and transactivation functions of GCs directed to different genes produce the beneficial effect of inflammatory inhibition. On the other hand, steroid-induced diabetes and glaucoma appear to be produced by the transactivation action of GCs on genes responsible for these diseases. H. Schäcke et al., *Pharmacol. Ther.*, Vol. 96, 23-43 (2002). Thus, while the transactivation of certain genes by GCs produces beneficial effects, the transactivation of other genes by the same GCs can produce undesired side effects. Therefore, in another aspect, the present invention provides pharmaceutical compositions for the treatment, reduction, alleviation, or amelioration of a pathological condition having an etiology in inflammation, which compositions avoid generation of one or more adverse side effects of GCs.

In one aspect, an adverse side effect of GCs is selected from the group consisting of glaucoma, cataract, hypertension, hyperglycemia, hyperlipidemia (increased levels of triglycerides), and hypercholesterolemia (increased levels of cholesterol). In one embodiment, a level of said at least an adverse side effect is determined at about one day after said compounds or compositions are first administered to, and are present in, said subject. In another embodiment, a level of said at least an adverse side effect is determined about 30 days after said compounds or compositions are first administered to, and are present in, said subject. Alternatively, a level of said at least an adverse side effect is determined about 2, 3, 4, 5, or 6 months after said compounds or compositions are first administered to, and are present in, said subject.

In another aspect, said at least a prior-art glucocorticoid used to treat or reduce the same condition or disorder is administered to said subject at a dose and a frequency sufficient to produce the same beneficial effect on said condition or disorder as a compound or composition of the present invention after about the same elapsed time.

In still another aspect, said at least a prior-art glucocorticoid is selected from the group consisting of 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clobetasone, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difluprednate, enoxolone, fluazacort, flucoronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortol, halcinonide, halobetasol propionate, halometasone, halopredone acetate, hydrocortarnate, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylamino-acetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, triamcinolone hexacetonide, their physiologically acceptable salts, combinations thereof, and mixtures thereof. In one embodiment, said at least a prior-art glucocorticoid is selected from the group consisting of dexamethasone, prednisone, prednisolone, methylprednisolone, medrysone, triamcinolone, loteprednol etabonate, physiologically acceptable salts thereof, combinations thereof, and mixtures thereof. In another embodiment, said at least a prior-art glucocorticoid is acceptable for ophthalmic uses.

TESTING FOR POTENTIAL SIDE EFFECTS

TLR or TLR coreceptor antagonists are not expected to generate side effects that have been seen with glucocorticoid therapy. However, such effects may still be assessed by a test disclosed below. One of the most frequent undesirable actions of a glucocorticoid therapy is steroid diabetes. The reason for this is the stimulation of gluconeogenesis in the liver by the induction of the transcription of hepatic enzymes involved in gluconeogenesis and metabolism of free amino acids that are produced from

the degradation of proteins (catabolic action of glucocorticoids). A key enzyme of the catabolic metabolism in the liver is the tyrosine aminotransferase ("TAT"). The activity of this enzyme can be determined photometrically from cell cultures of treated rat hepatoma cells. Thus, the gluconeogenesis by a glucocorticoid can be compared to that of a TLR or TLR coreceptor antagonist by measuring the activity of this enzyme. For example, in one procedure, the cells are treated for 24 hours with the test substance (a TLR or TLR coreceptor antagonist, or a glucocorticoid), and then the TAT activity is measured. The TAT activities for the selected TLR or TLR coreceptor antagonist and glucocorticoid are then compared. Other hepatic enzymes can be used in place of TAT, such as phosphoenolpyruvate carboxykinase, glucose-6-phosphatase, or fructose-2,6-biphosphatase. Alternatively, the levels of blood glucose in an animal model may be measured directly and compared for individual subjects that are treated with a glucocorticoid for a selected condition and those that are treated with a TLR or TLR coreceptor antagonist for the same condition.

Another undesirable result of glucocorticoid therapy is increased IOP in the subject. IOP of subjects treated with a glucocorticoid or a TLR or TLR coreceptor antagonist for a condition may be measured directly and compared.

Benefits of a composition of the present invention for neuroprotection can be determined, judged, estimated, or inferred by conducting assays and measurements, for example, to determine: (1) the protection of nerve cells from glutamate induced toxicity; and/or (2) the neural protection in a nerve crush model of mechanical injury. Non-limiting examples of such assays and measurements are disclosed in US Patent 6,194,415; which is incorporated herein by reference.

SEQUENCE LISTING

<110> Bausch & Lomb Incorporated
 <120> Compositions Comprising Toll-Like Receptor Or Coreceptor
 Antagonists and Methods for Ocular Neuroprotection
 <130> P04590
 <160> 29
 <170> PatentIn version 3.4
 <210> 1
 <211> 6
 <212> DNA

<213> Homo sapiens	
<400> 1	6
ttaggg	
<210> 2	
<211> 15	
<212> DNA	
<213> Synthetic	
<400> 2	15
tcctggcggg gaagt	
<210> 3	
<211> 15	
<212> DNA	
<213> Synthetic	
<400> 3	15
tcctaacggg gaagt	
<210> 4	
<211> 15	
<212> DNA	
<213> Synthetic	
<400> 4	15
tcctggaggg gttgt	
<210> 5	
<211> 15	
<212> DNA	
<213> Synthetic	
<400> 5	15
tcctggcggg caagt	
<210> 6	
<211> 15	
<212> DNA	
<213> Synthetic	
<400> 6	15
tcctggcggg taagt	
<210> 7	
<211> 15	
<212> DNA	
<213> Synthetic	
<400> 7	15
tcctggcggg aaagt	
<210> 8	
<211> 15	
<212> DNA	
<213> Synthetic	
<400> 8	15
tcctgcaggg taagt	

<210> 9
 <211> 5
 <212> PRT
 <213> Mus musculus

<400> 9

Asp Ser Tyr Ile His
 1 5

<210> 10
 <211> 17
 <212> PRT
 <213> Mus musculus

<400> 10

Trp Thr Asp Pro Glu Asn Val Asn Ser Ile Tyr Asp Pro Arg Phe Gln
 1 5 10 15

Gly

<210> 11
 <211> 11
 <212> PRT
 <213> Mus musculus

<400> 11

Gly Tyr Asn Gly Val Tyr Tyr Ala Met Asp Tyr
 1 5 10

<210> 12
 <211> 5
 <212> PRT
 <213> Mus musculus

<400> 12

Asp Tyr Trp Ile Glu
 1 5

<210> 13
 <211> 17
 <212> PRT
 <213> Mus musculus

<400> 13

Glu Ile Leu Pro Gly Ser Gly Ser Thr Asn Tyr Asn Glu Asp Phe Lys
 1 5 10 15

Asp

<210> 14
 <211> 9
 <212> PRT
 <213> Mus musculus

<400> 14

Glu Glu Arg Ala Tyr Tyr Phe Gly Tyr

1 5

<210> 15
 <211> 6
 <212> PRT
 <213> Mus musculus

<400> 15

Gly Gly Tyr Ser Trp His
 1 5

<210> 16
 <211> 16
 <212> PRT
 <213> Mus musculus

<400> 16

Tyr Ile His Tyr Ser Gly Tyr Thr Asp Phe Asn Pro Ser Leu Lys Thr
 1 5 10 15

<210> 17
 <211> 9
 <212> PRT
 <213> Mus musculus

<400> 17

Lys Asp Pro Ser Asp Gly Phe Pro Tyr
 1 5

<210> 18
 <211> 7
 <212> PRT
 <213> Mus musculus

<400> 18

Thr Tyr Asn Ile Gly Val Gly
 1 5

<210> 19
 <211> 16
 <212> PRT
 <213> Mus musculus

<400> 19

His Ile Trp Trp Asn Asp Asn Ile Tyr Tyr Asn Thr Val Leu Lys Ser
 1 5 10 15

<210> 20
 <211> 11
 <212> PRT
 <213> Mus musculus

<400> 20

Met Ala Glu Gly Arg Tyr Asp Ala Met Asp Tyr
 1 5 10

<210> 21	
<211> 15	
<212> DNA	
<213> Artificial Sequence	
<220>	
<223> synthetic oligonucleotide	
<400> 21	
tcctggcggg gaagt	15
<210> 22	
<211> 15	
<212> DNA	
<213> Artificial Sequence	
<220>	
<223> synthetic oligonucleotide	
<400> 22	
gcctggcggg gaagt	15
<210> 23	
<211> 15	
<212> DNA	
<213> Artificial Sequence	
<220>	
<223> synthetic oligonucleotide	
<400> 23	
acctggcggg gaagt	15
<210> 24	
<211> 15	
<212> DNA	
<213> Artificial Sequence	
<220>	
<223> synthetic oligonucleotide	
<400> 24	
ccctggcggg gaagt	15
<210> 25	
<211> 15	
<212> DNA	
<213> Artificial Sequence	
<400> 25	
tcccggcggg gaagt	15
<210> 26	
<211> 15	
<212> DNA	
<213> Artificial Sequence	
<220>	
<223> synthetic oligonucleotide	
<400> 26	
tccaccaccc caagt	15

<210> 27
 <211> 14
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> synthetic oligonucleotide

 <400> 27
 cctggcgggg aagt 14

<210> 28
 <211> 15
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> synthetic oligonucleotide

 <400> 28
 tcctagcggg gaagt 15

<210> 29
 <211> 15
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> synthetic oligonucleotide

 <400> 29
 tcctggaggg gaagt 15

While specific embodiments of the present invention have been described in the foregoing, it will be appreciated by those skilled in the art that many equivalents, modifications, substitutions, and variations may be made thereto without departing from the spirit and scope of the invention as defined in the appended claims.

WHAT IS CLAIMED IS:

1. A composition comprising an antagonist to at least a human TLR, an antagonist to at least a coreceptor of human TLR, a compound that is capable of inhibiting an activation of a human TLR signaling pathway, or a combination thereof; wherein said antagonist, compound, or combination thereof is present at a concentration such that the composition is capable of treating or controlling degeneration of at least a component of an optic nerve system in a subject.
2. The composition of claim 1, further comprising an anti-inflammatory medicament.
3. The composition of claim 1, wherein said degeneration is a result of a disease selected from the group consisting of glaucoma, AMD, DR, retinitis pigmentosa, and combinations thereof.
4. The composition of claim 1, wherein said at least a human TLR is selected from the group consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, and combinations thereof.
5. The composition of claim 1, wherein said at least a human TLR is selected from the group consisting of TLR2, TLR3, TLR4, TLR8, TLR9, and combinations thereof.
6. The composition of claim 1, wherein said at least a coreceptor of human TLR comprises CD14, MD-2, a combination thereof, or a mixture thereof.
7. The composition of claim 1, wherein said antagonist or said compound is selected from the group consisting of anti-human antibodies of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, CD14, or MD-2; and combinations thereof.

8. The composition of claim 1, wherein said compound that is capable of inhibiting an activation of a human TLR signaling pathway comprises a soluble form of an extracellular domain of a human TLR that recognizes a moiety of a compound that is generated by stressor acting on cells or components of an optic nerve system.

9. The composition of claim 1, wherein said compound that is capable of inhibiting an activation of a human TLR signaling pathway comprises at least a soluble form of CD14 or MD-2.

10. The composition of claim 1, wherein said antagonist or said compound comprises an antibody of a TLR, wherein said antibody comprises a heavy-chain complimentary determining region having an amino acid sequence selected from the group consisting of SEQ. NO. 9 – SEQ.NO. 20 and combinations thereof.

11. The composition of claim 1, wherein said antagonist or compound comprises a nucleotide sequence selected from the group consisting of SEQ. NO. 1 – SEQ. NO. 8, SEQ. NO. 21 – SEQ. NO. 29, and combinations thereof.

12. The composition of claim 1, wherein said antagonist or compound comprises a nucleotide sequences comprising multiple repeats of any one of SEQ. NO. 1 – SEQ. NO. 8, SEQ. NO. 21 – SEQ. NO. 29, and combinations thereof.

13. The composition of claim 12, wherein said nucleotide sequence comprises two, three, four, or five repeats of any one of SEQ. NO. 1 – SEQ. NO. 8, SEQ. NO. 21 – SEQ. NO. 29, and combinations thereof.

14. The composition of claim 1, wherein said antagonist or compound comprises a material selected from the group consisting of chloroquine, hydroxychloroquine, quinacrine, 9-aminoacridine, 4-aminoquinoline, and a mixture thereof.

15. The composition of claim 1, wherein said antagonist or compound comprises a ligand of vitamin D receptor.

16. The composition of claim 15, wherein said ligand of vitamin D receptor comprises vitamin D or an analogue thereof.
17. The composition of claim 15, wherein said ligand of vitamin D receptor comprises vitamin D₂, vitamin D₃, or a mixture thereof.
18. The composition of claim 1, wherein said antagonist or compound comprises a compound having one of Formulae I through XXII.
19. The composition of claim 1, wherein said antagonist or said compound is present in an amount in a range from about 0.0001 to about 10 percent by weight of said composition.
20. The composition of claim 2, wherein said anti-inflammatory medicament comprises a material selected from the group consisting of non-steroidal anti-inflammatory drugs, peroxisome proliferator-activated receptor ("PPAR") ligands, and combinations thereof.
21. The composition of claim 20, wherein said anti-inflammatory medicament comprises an antihistamine selected from the group consisting of PPAR α ligands, PPAR δ ligands, PPAR γ ligands, and combinations thereof.
22. The composition of claim 1, further comprising a medicament selected from the group consisting of immunosuppressants, cyclooxygenase-2 inhibitors, DMARDS (disease-modifying anti-rheumatic drugs), anti-cell adhesion molecules, and combinations thereof.
23. The composition of claim 22, wherein said immunosuppressants are selected from the group consisting of cyclosporine, tacrolimus, rapamycinazathioprine, 6-mercaptopurine, and combinations thereof.
24. The composition of claim 1, wherein the composition has a pH in a range from about 5 to about 8.

25. The composition of claim 24, wherein the composition has a pH in a range from about 6.5 to about 7.8.

26. A composition comprising: (a) an antagonist to at least a human TLR, an antagonist to at least a coreceptors of human TLR, a compound that is capable of inhibiting an activation of a human TLR signaling pathway, or a combinations thereof; and (b) an additional medicament selected from the group consisting of NSAIDs, PPAR ligands, immunosuppressants, cyclooxygenase-2 inhibitors, DMARDS, anti-cell adhesion molecules, and combinations thereof; wherein the composition is capable of treating or controlling degeneration of a component of an optic nerve system; wherein each of said at least a human TLR comprises TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, or a combination thereof; said at least a coreceptors of human TLR comprises CD14, MD-2, a combination thereof, or a mixture thereof; said antagonist or compound; and said additional medicament, when present, is present in an amount from about 0.0001 to about 5 percent by weight of said composition; and said composition has a pH of about 5-8.

27. A method for treating or controlling degeneration of a component of an optic nerve system in a subject, the method comprising administering to an environment of an affected eye a pharmaceutically effective amount of a composition that comprises an antagonist to at least a human TLR, an antagonist to at least a coreceptor of human TLR, a compound that is capable of inhibiting an activation of a human TLR signaling pathway, or a combination thereof, wherein said composition is administered at a frequency effective to provide said treating or controlling.

28. The method of claim 27, wherein said degeneration is a result of a disease selected from the group consisting of glaucoma, AMD, DR, retinitis pigmentosa, and combinations thereof.

29. The method of claim 28; wherein said at least a human TLR comprises TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, or a combination thereof; and said at least a coreceptor of human TLR comprises CD14, MD-2, a combination thereof, or a mixture thereof.

30. The method of claim 28, wherein said antagonist or said compound is selected from the group consisting of anti-human antibodies of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, CD14, or MD-2; and combinations thereof.

31. The method of claim 28, wherein said compound that is capable of inhibiting an activation of a human TLR signaling pathway comprises a soluble form of an extracellular domain of a human TLR that recognizes a moiety of a compound that is generated as a result of stress on the optic nerve system, or a soluble form of CD14 or MD-2.

32. The method of claim 28, wherein said antagonist or compound comprises a nucleotide sequence selected from the group consisting of SEQ. NO. 1 – SEQ. NO. 8, SEQ. NO. 21 – SEQ. NO. 29, and combinations thereof.

33. The method of claim 28, wherein said antagonist or compound comprises a nucleotide sequences comprising multiple repeats of any one of SEQ. NO. 1 – SEQ. NO. 8, SEQ. NO. 21 – SEQ. NO. 29, and combinations thereof.

34. The method of claim 33, wherein said nucleotide sequence comprises two, three, four, or five repeats of any one of SEQ. NO. 1 – SEQ. NO. 8, SEQ. NO. 21 – SEQ. NO. 29, and combinations thereof.

35. The method of claim 28, wherein said antagonist or said compound comprises a compound having one of Formulae I through XXII.

36. The method of claim 28, wherein said antagonist or said compound comprises an antibody of a TLR, wherein said antibody comprises a heavy-chain complimentary determining region having an amino acid sequence selected from the group consisting of SEQ. NO. 9 – SEQ.NO. 20 and combinations thereof.

37. The method of claim 28, wherein said antagonist or compound comprises a material selected from the group consisting of chloroquine, hydroxychloroquine, quinacrine, 9-aminoacridine, 4-aminoquinoline, and a mixture thereof.

38. The method of claim 28, wherein said antagonist or compound comprises a ligand of vitamin D receptor.

39. The method of claim 38, wherein said ligand of vitamin D receptor comprises vitamin D or an analogue thereof.

40. The method of claim 38, wherein said ligand of vitamin D receptor comprises vitamin D₂, vitamin D₃, or a mixture thereof.

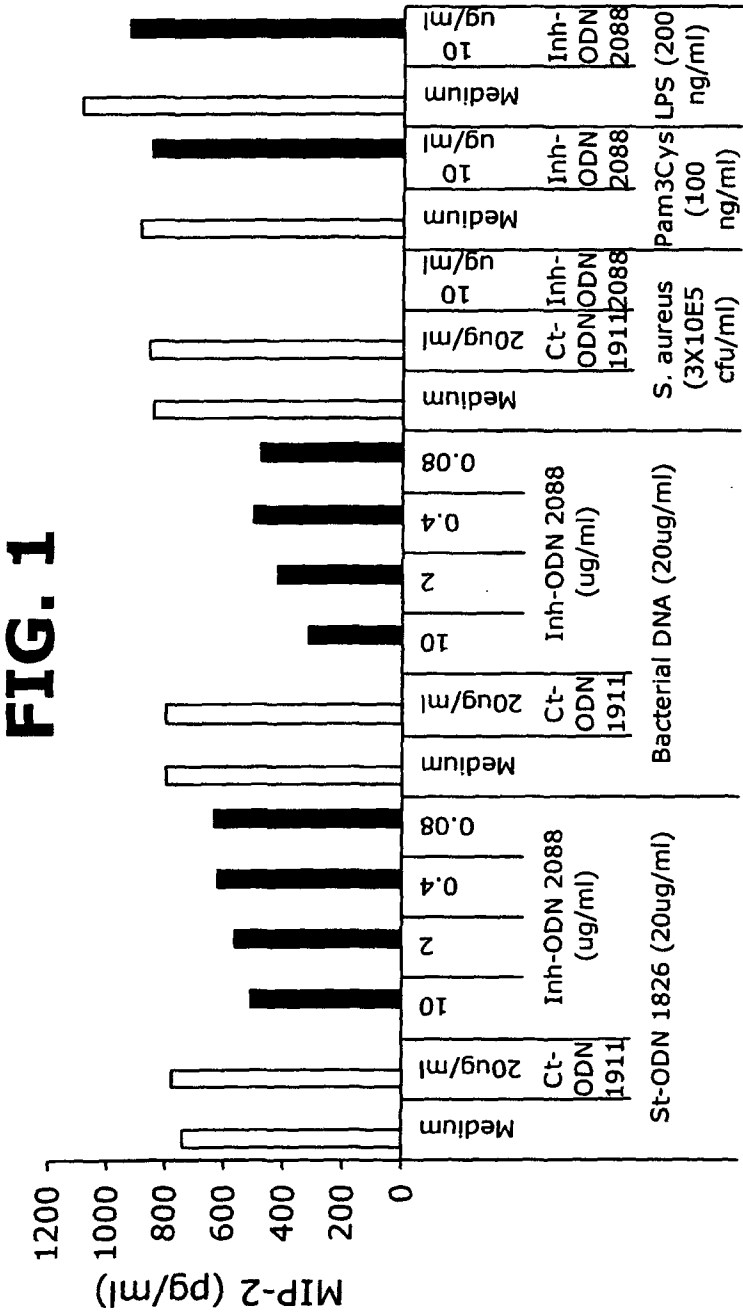
41. The method of claim 28, wherein said antagonist or said compound is present in an amount in a range from about 0.0001 to about 5 percent by weight of said composition.

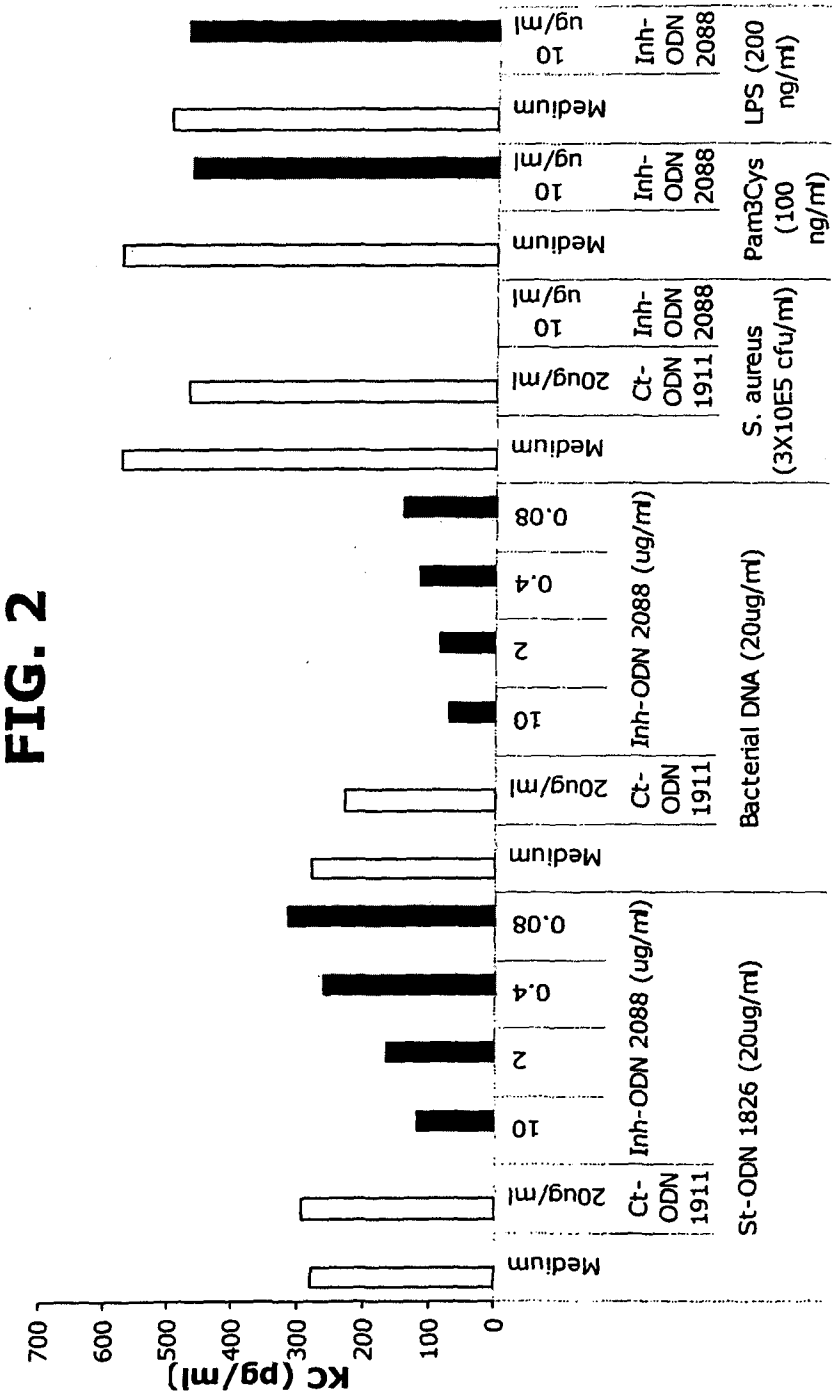
42. The method of claim 28, wherein the composition further comprises an additional medicament selected from the group consisting of NSAIDs, PPAR ligands, immunosuppressants, cyclooxygenase-2 inhibitors, DMARDS, anti-cell adhesion molecules, and combinations thereof; wherein said additional medicament is present in an amount from about 0.0001 to about 5 weight percent.

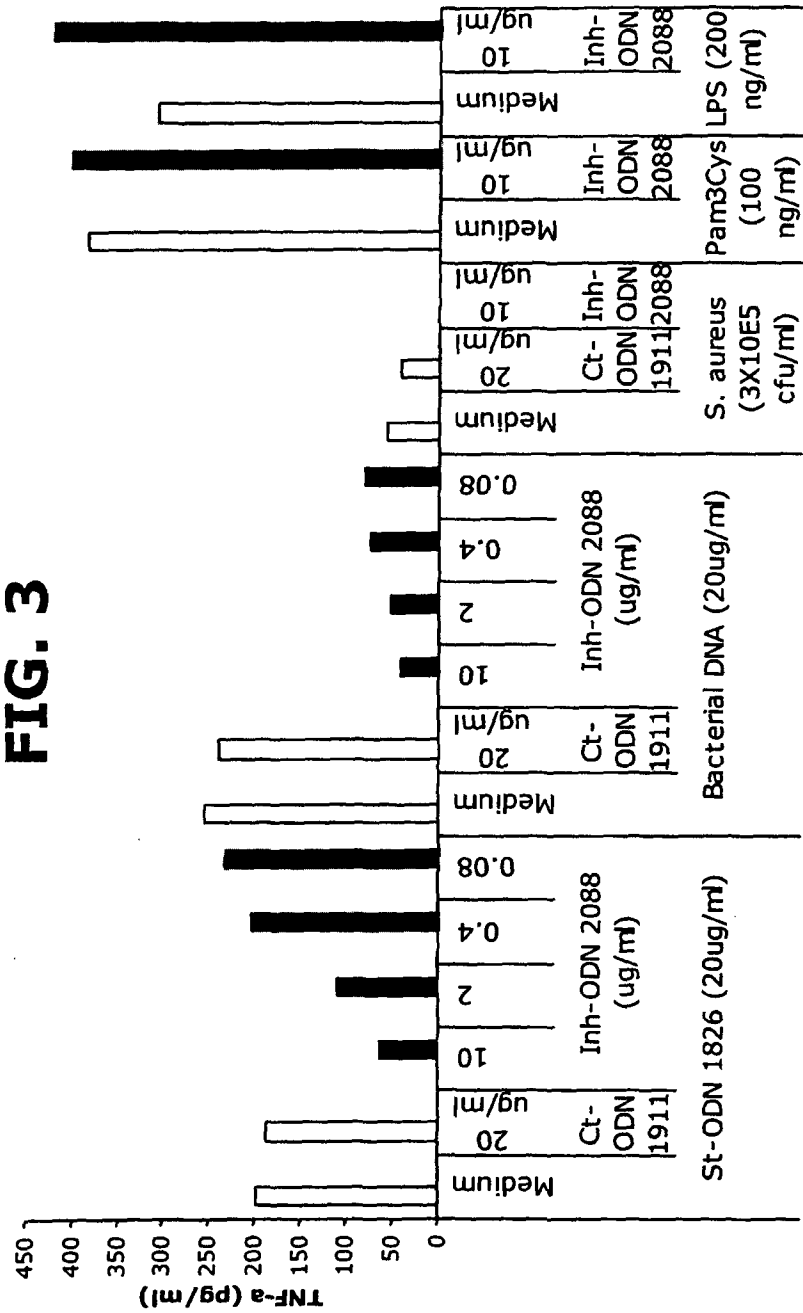
43. The method of claim 42, wherein said additional medicament comprises an immunosuppressant selected from the group consisting of cyclosporine, tacrolimus, rapamycinazathioprine, 6-mercaptopurine, and combinations thereof.

44. A method for preparing a composition for treating or controlling degeneration of a component of an optic nerve system, the method comprising combining an antagonist to at least a human TLR, an antagonist to at least a coreceptor of human TLR, a compound that is capable of inhibiting an activation of a human TLR signaling pathway, or a combination thereof with a pharmaceutically acceptable carrier; wherein said antagonist, compound, or combination thereof is present at a concentration such that the composition is capable of treating or controlling said degeneration in a subject.

45. The method of claim 44, further comprising adding a medicament selected from the group consisting of NSAIDs, PPAR ligands, immunosuppressants, cyclooxygenase-2 inhibitors, DMARDS, anti-cell adhesion molecules, and combinations thereof to the composition.







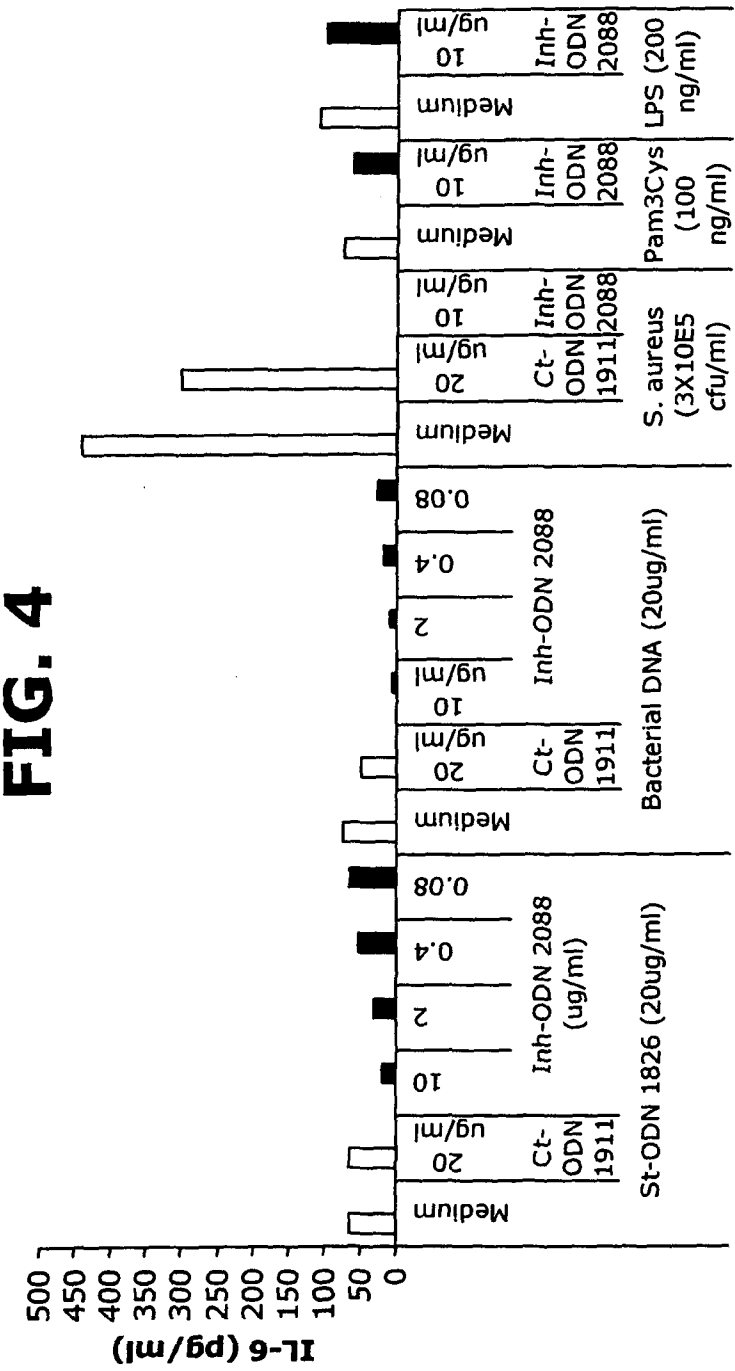


FIG. 5

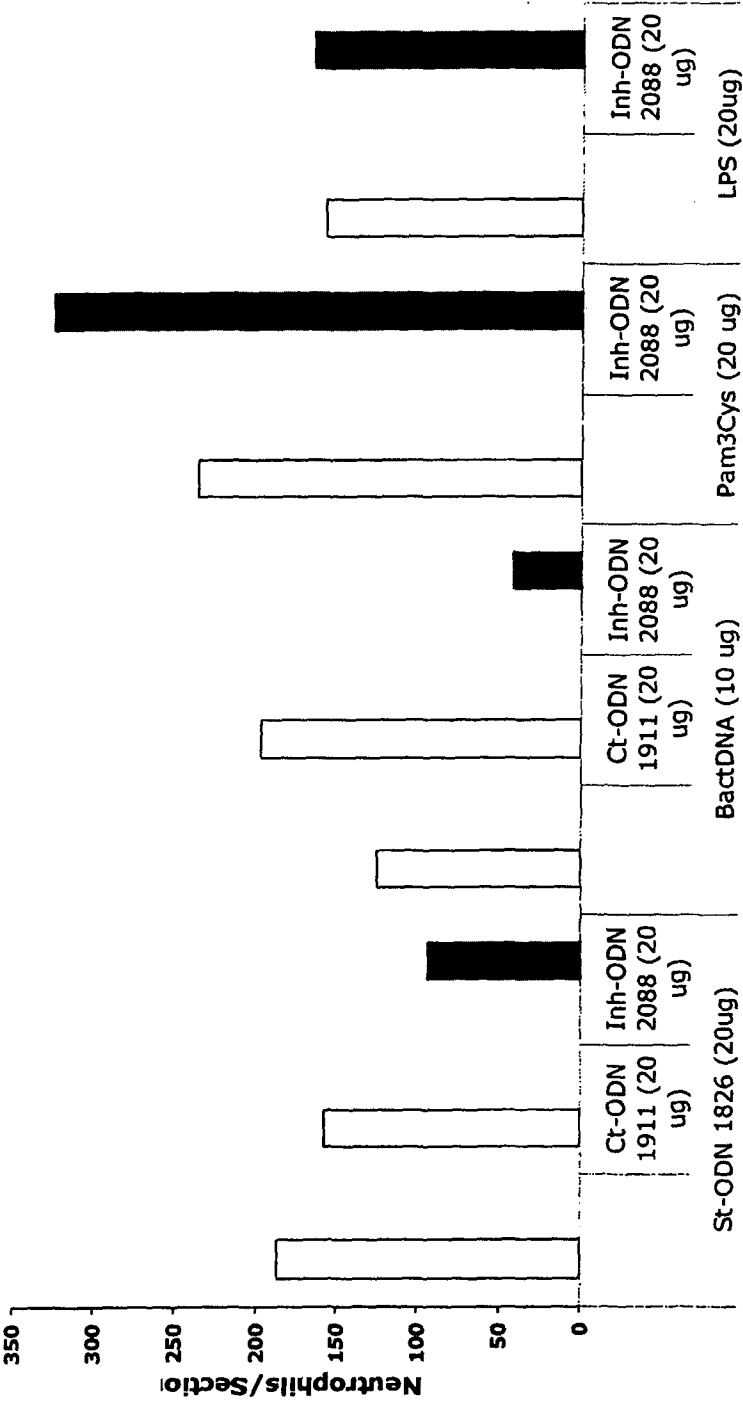


FIG. 6

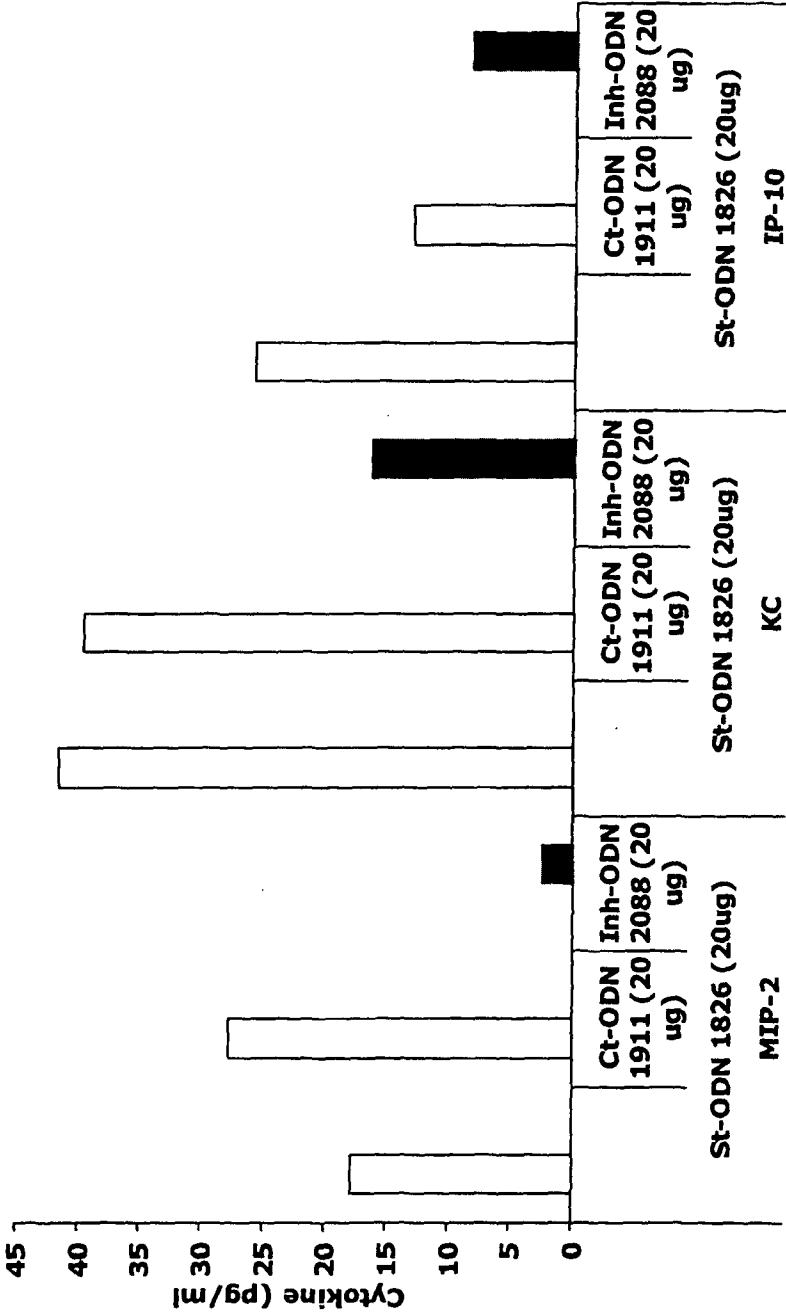


FIG. 7

