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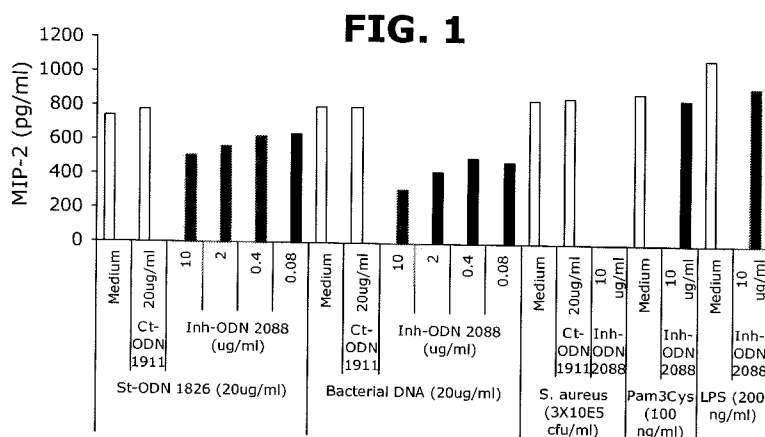
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(54) Title: COMPOSITIONS AND METHODS FOR TREATING OR CONTROLLING INFECTIONS AND SEQUELAE THEREOF



(57) Abstract: Compositions for treating or controlling an infection and sequelae thereof comprise an antagonist to a toll-like receptor ("TLR"), a coreceptor thereof, or a combination thereof, and an anti-infective agent. The compositions can also include another anti-inflammatory medicament.

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COMPOSITIONS AND METHODS FOR TREATING OR CONTROLLING INFECTIONS AND SEQUELAE THEREOF

BACKGROUND

The present invention relates to compositions for treating or controlling infections and sequelae thereof. In particular, the present invention relates to pharmaceutical compositions that comprise an anti-infective medicament and an inhibitor of, or antagonist to, a toll-like receptor ("TLR") or a TLR coreceptor, for the treatment or control of infection of a tissue of the eye and sequelae thereof. In addition, the present invention relates to methods for treating or controlling infections and sequelae thereof using such compositions.

The interface between the body and its environment is large, and thus presents many potential opportunities for invasion by environmental virulent pathogens. The outer tissues of the eye constitute parts of this interface, and thus, the eye and its surrounding tissues are also vulnerable to virulent microorganisms, the invasion and uncontrolled growth of which cause various types of ophthalmic infections, such as blepharitis, conjunctivitis, keratitis, or trachoma, which can result in serious impairment of vision if untreated. The common types of microorganisms causing ophthalmic infections are viruses, bacteria, and fungi. These microorganisms may directly invade the surface of the eye, or permeate into the globe of the eye through trauma or surgery, or transmit into the eye through the blood stream or lymphatic system as a consequence of a systemic disease. The microorganisms may attack any part of the eye structure, including the conjunctiva, the cornea, the uvea, the vitreous body, the retina, and the optic nerve. Ophthalmic infections can cause severe pain, swollen and red tissues in or around the eye, and blurred and decreased vision.

Host defense against challenge by foreign materials is elicited by the immune system, which consists of innate immunity and acquired (adaptive) immunity. Acquired immunity is mediated by T and B lymphocytes that proliferate clonally in response to a specific pathogen or antigen. The generation of acquired immune responses requires a number of days after the host is exposed to the challenge. In contrast, the innate immune system is activated soon after such pathogenic or antigenic challenge to provide

nonspecific protection before the acquired immunity system becomes fully effective.

It was recently discovered that the rapid innate immune response is due in part to a family of cellular receptors termed “Toll-like receptors” (“TLRs”) that have evolved to recognize some common structural features of the diverse microorganisms, which features are referred to as “pathogen-associated molecular patterns” (or “PAMPs”). To date, at least ten mammalian TLRs 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). 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. J.H. Chang et al., *Br. J. Ophthalmol.*, Vol. 90, 103(2006).

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 proinflammatory 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).

The body's innate cascade is activated soon after invasion by a foreign pathogen begins. Circulating leukocytes (neutrophils, eosinophils, basophils, monocytes, and macrophages), which express TLR1-TLR10; and mast cells, which reside in connective tissues in close proximity to epithelial surfaces and express TLR2, TLR3, TLR4, TLR7, and TLR9, comprise the first line of host defense against invading pathogen. See; e.g., Hayashi et al., *Blood*, Vol. 102, 2660 (2003); Muzio et al., *J. Immunol.*, Vol. 164, 5998 (2000); V. Supajatura et al., *J. Clin. Invest.*, Vol. 109, No. 10, 1351 (2002); and H. Matsushima et al., *J. Immunol.*, Vol. 173, No. 1, 531-541 (2004).

Pathogenic ligands bound to TLRs of mast cells activate them to release a wide range of preformed cytokines, such as TNF- α , IL-1 β , IL-4, IL-5, IL-6, and IL-13, or to stimulate additional production and release of these cytokines. See V. Supajatura et al., *supra*. Moreover, leukocytes and some affected tissue cells are activated by pathogens to synthesize and release proinflammatory 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 infected site, amplifying the response of the immune system to defend the host against the foreign pathogen by attempting to eliminate the foreign pathogen through phagocytosis. 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 proinflammatory 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 pathogens from the site of infection, 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 injured site 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. Therefore, a prolonged or overactive inflammation should be controlled to limit the unintended damages to the body and to hasten the body's recovery process.

Glucocorticoids (also referred to herein as "corticosteroids") represent one of the most effective clinical treatment for a range of inflammatory conditions, including acute inflammation. However, steroidal drugs can have side effects that threaten the overall health of the patient.

It is known that certain glucocorticoids have a greater potential for elevating intraocular pressure ("IOP") than other compounds in this class. For example, it is known that prednisolone, which is a very potent ocular anti-inflammatory agent, has a greater tendency to elevate IOP than fluorometholone, which has moderate ocular anti-inflammatory activity. It is also known that the risk of IOP elevations associated with the topical ophthalmic use of glucocorticoids increases over time. In other words, the chronic (i.e., long-term) use of these agents increases the risk of significant IOP elevations. Unlike acute ocular inflammation associated with physical trauma or infection of the outer surface of the anterior portion of the eye, which requires short-term therapy on the order of a few weeks, infection and inflammation of the posterior portion of the eye can require treatment for extended periods of time, generally several months or more. This chronic use of corticosteroids significantly increases the risk of IOP elevations. In addition, use of corticosteroids is also known to increase the risk of cataract formation in a dose- and duration-dependent manner. Once cataracts develop, they may progress despite discontinuation of corticosteroid therapy.

Chronic administration of glucocorticoids also can lead to drug-induced osteoporosis by suppressing intestinal calcium absorption and inhibiting bone formation. Other adverse side effects of chronic administration of glucocorticoids include hypertension, hyperglycemia, hyperlipidemia (increased levels of triglycerides) and hypercholesterolemia (increased levels of cholesterol) because of the effects of these drugs on the body metabolic processes.

Therefore, there is a continued need to provide improved pharmaceutical compositions and methods for treating or controlling infections and their sequelae.

SUMMARY

In general, the present invention provides compositions and methods for treating or controlling infections and sequelae thereof.

In one aspect, the present invention provides compositions and methods for treating or controlling infections of a tissue of the eye and sequelae thereof.

In another aspect, said infections are selected from the group consisting of conjunctivitis, blepharitis, cellulitis, keratitis, corneal ulcer, trachoma, and combinations thereof.

In still another aspect, a composition of the present invention comprises at least a first active ingredient and a second active ingredient, wherein the first active ingredient 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, coreceptor of a TLR (such an inhibitor or antagonist hereinafter sometimes referred to as "TLR-coreceptor antagonist"), or a combination thereof; and the second active ingredient comprises an anti-infective agent; wherein the active ingredients are present in amounts effective for treating or controlling an infection of a tissue of the eye and sequelae thereof.

In yet another aspect, said sequelae comprise inflammation of a tissue of the eye.

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

In still another aspect, such a TLR is expressed in or on a cell associated with an ocular tissue or a tissue adjacent to an eye.

In yet another aspect, such a TLR is expressed in a mast cell in a tissue of the eye.

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, said anti-infective agent comprises an antibacterial drug, an antifungal drug, an antiviral drug, an antiprotozoal drug, or a combination thereof.

In yet another aspect, the present invention provides a method for treating or controlling in a subject an infection and sequelae thereof in a subject. The method comprises applying a composition to said subject, wherein the composition comprises at least a first active ingredient and a second active ingredient, wherein the first active ingredient comprises an inhibitor of an activity of, or an antagonist to, at least a toll-like receptor; or an inhibitor of, or an antagonist to, coreceptor of a TLR; or a combination thereof; and the second active ingredient comprises an anti-infective agent; wherein the active ingredients are present in amounts effective for treating or controlling an infection of a tissue of the eye and sequelae thereof.

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

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 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

In general, the present invention provides pharmaceutical compositions and methods for treating or controlling infections and sequelae thereof.

In one aspect, the present invention provides compositions and methods for treating or controlling infections of a tissue of the eye and sequelae thereof.

In another aspect, said infections are selected from the group consisting of conjunctivitis, blepharitis, cellulitis, keratitis, corneal ulcer, trachoma, and combinations thereof.

In still another aspect, said infections comprise conjunctivitis, keratitis, or a combination thereof.

In yet another aspect, said infections comprise conjunctivitis.

In still another aspect, a composition of the present invention comprises at least a first active ingredient and a second active ingredient, wherein the first active ingredient comprises an inhibitor of an activity of, or an antagonist to, at least a TLR antagonist; or TLR-coreceptor antagonist, or a combination thereof; and the second active ingredient comprises an anti-infective agent; wherein the active ingredients are present in amounts effective for treating or controlling an infection of a tissue of the eye and sequelae thereof.

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

In yet another aspect, said sequelae comprise inflammation of a tissue of the eye.

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

In still another aspect, such a TLR is expressed in or on a cell associated with an ocular tissue or a tissue adjacent to an eye.

In yet another aspect, such a TLR is expressed in a mast cell in a tissue of the eye.

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, said anti-infective agent comprises an antibacterial drug, an antifungal drug, an antiviral drug, an antiprotozoal drug, or a combination thereof. Details regarding anti-infective agents suitable to be included in a composition and used in a method of the present invention are disclosed below.

In 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 a further aspect, said at least one human TLR is selected from the group consisting of TLR2, TLR4, TLR9, 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 still another embodiment, such an antagonist is a recombinant antibody of TLR2, TLR4, TLR9, CD14, MD-2, or a combination 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 microbe-expressed molecular structure ("MEMS"). By binding to an MEMS, a sTLR renders it unavailable for binding to the corresponding TLR and activating the signaling cascade involving the same. 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 MEM 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: TCCTAACGGGGGAAGT (SEQ. NO. 3), TCCTGGAGGGGGTTGT (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.

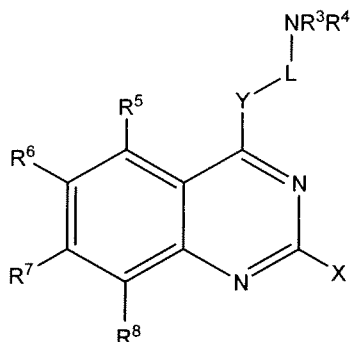
In still another embodiment, a composition of the present invention comprises a TLR-inhibiting ODN that comprises two, three, four, five, or more repeats of any one of SEQ. NO. 2 – SEQ. NO. 8, SEQ. NO. 21 – SEQ. NO. 29, or a combination thereof.

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-κB. *Id.* Thus, activated VDR or vitamin D₃ have been shown to inhibit the expression of proinflammatory 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.



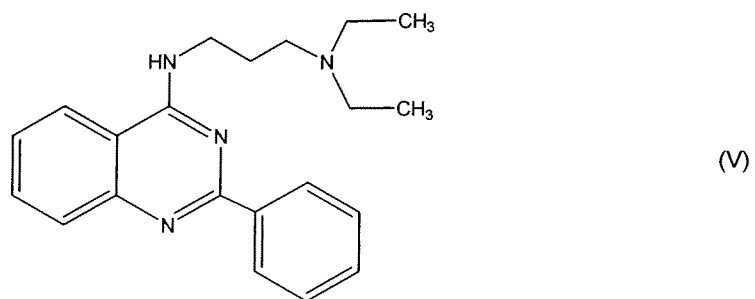
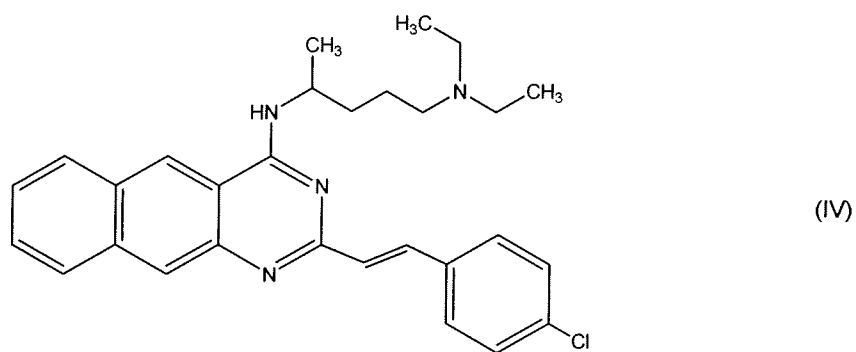
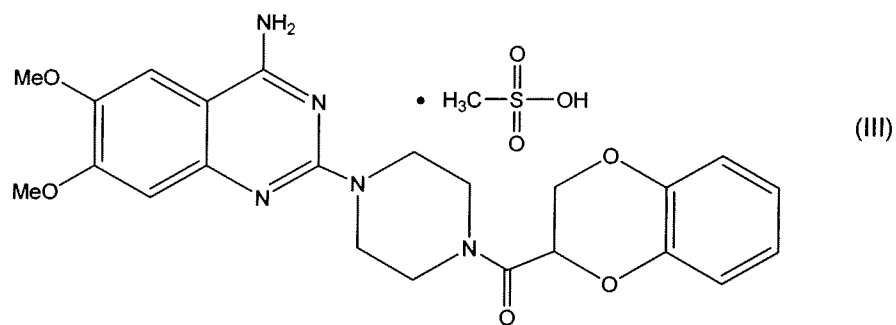
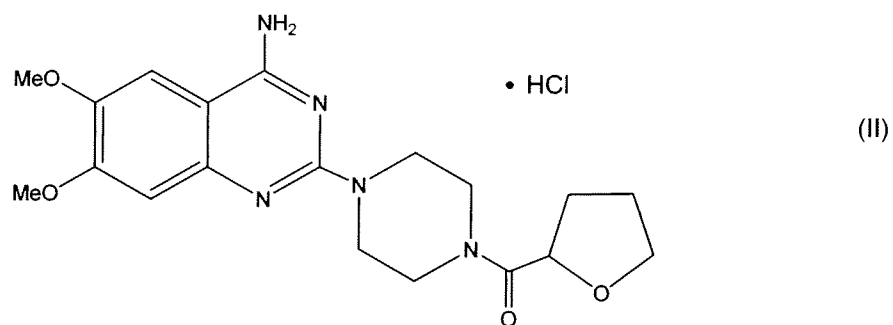
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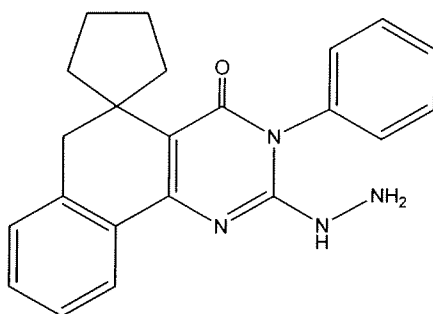
wherein X is a substituted or unsubstituted aryl, alkyl, heterocyclic, or styryl group, optionally attached to the quinazoline by a nitrogen, oxygen, or sulfur atom or by a SO or SO₂ group; Y is absent or is an oxygen atom, a sulfur atom, CR⁹R¹⁰, or NR¹¹, wherein R⁹, R¹⁰, and R¹¹ are each independently 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.

In certain embodiments, R⁹, R¹⁰, and R¹¹ are each independently a hydrogen atom or a C₁-C₅ (or C₁-C₃) alkyl, C₂-C₅ (or C₂-C₃) alkenyl, or C₅-C₁₄ (or C₅-C₁₀) aryl group.

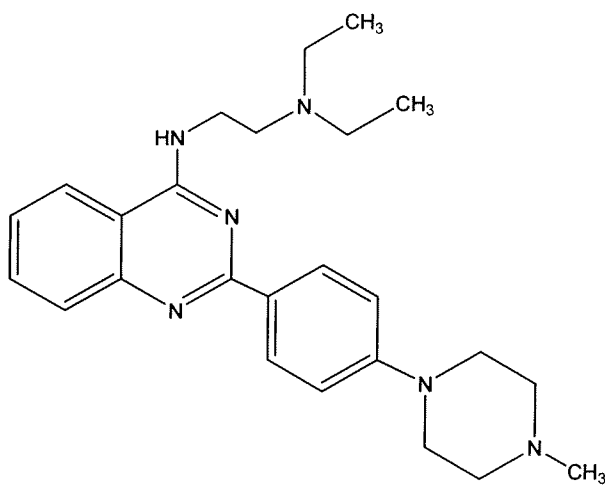
In certain other embodiments, R⁵, R⁶, R⁷, and R⁸ are each independently a hydrogen atom, a halogen atom, or a C₁-C₅ (or C₁-C₃) alkyl, C₂-C₅ (or C₂-C₃) alkenyl, C₅-C₁₄ (or C₅-C₁₀) aryl, or a 5-10 (or 5-7) membered heterocyclic group.

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

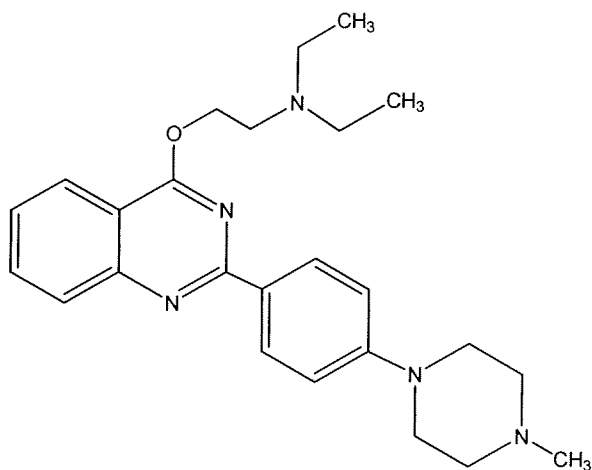




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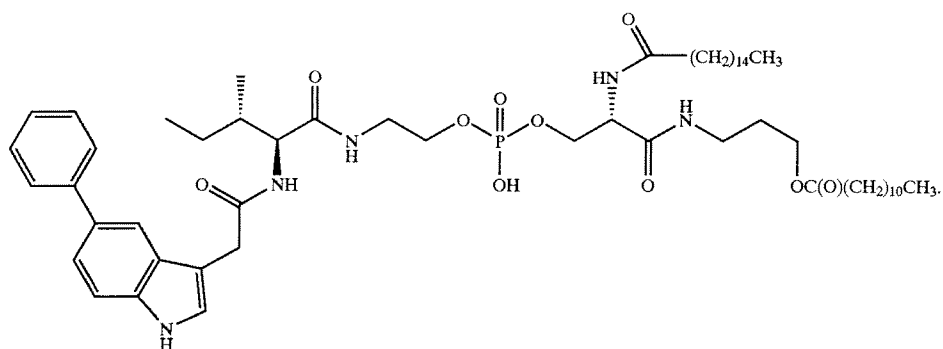


(VII)

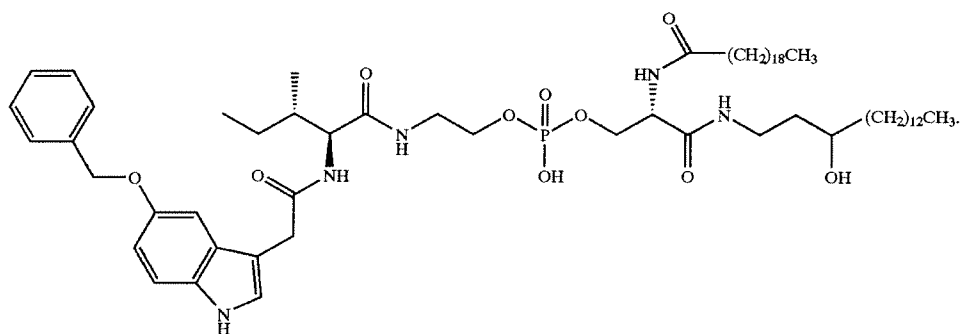


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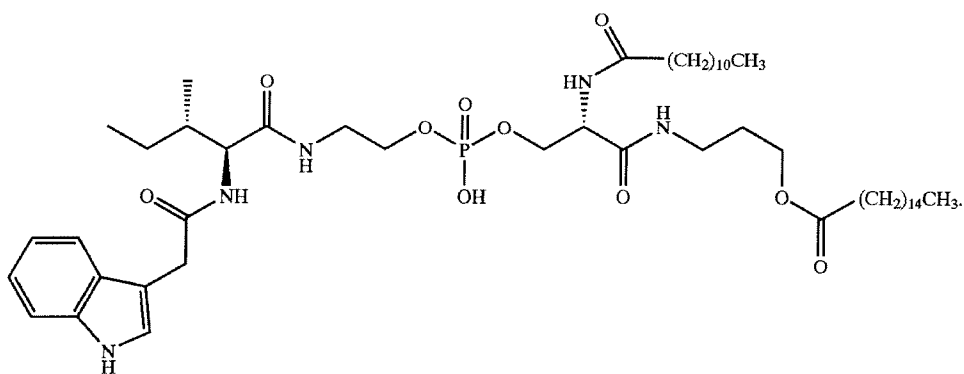
In still another aspect, a composition of the present invention comprises an antagonist to TLR2 receptor, as disclosed in US Patent Application Publication 2005/0113345, which is incorporated herein by reference. Non-limiting examples of such an antagonist include the following compounds.



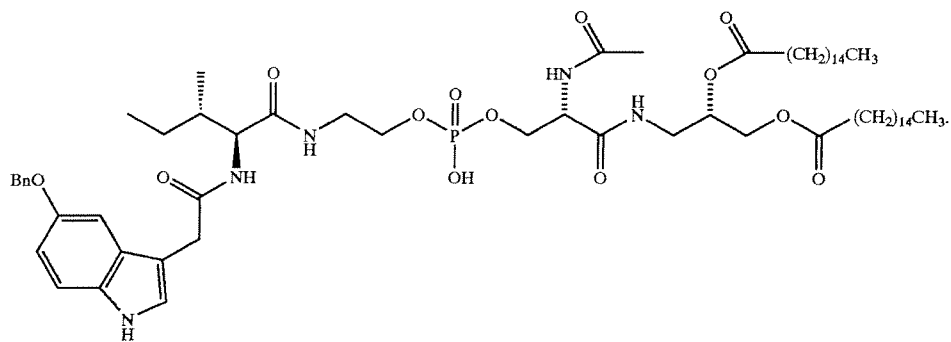
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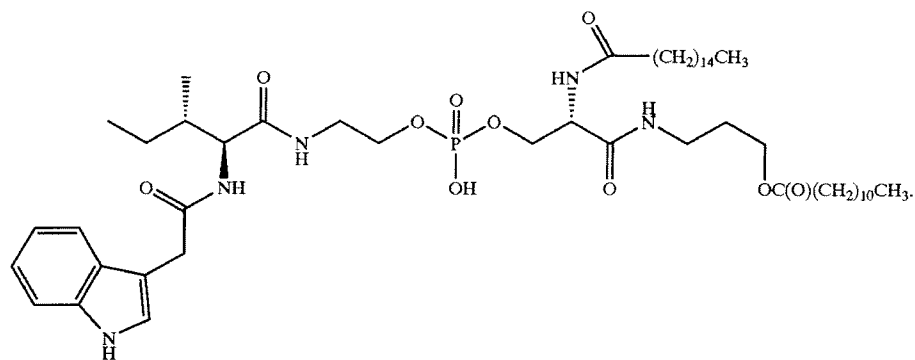
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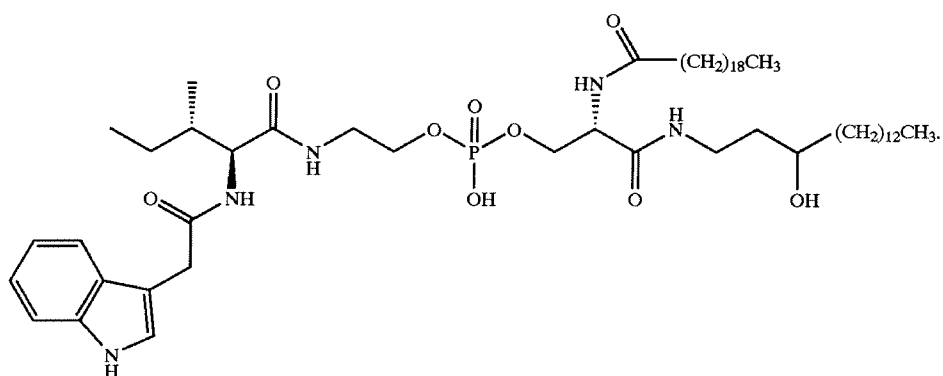
(XI)



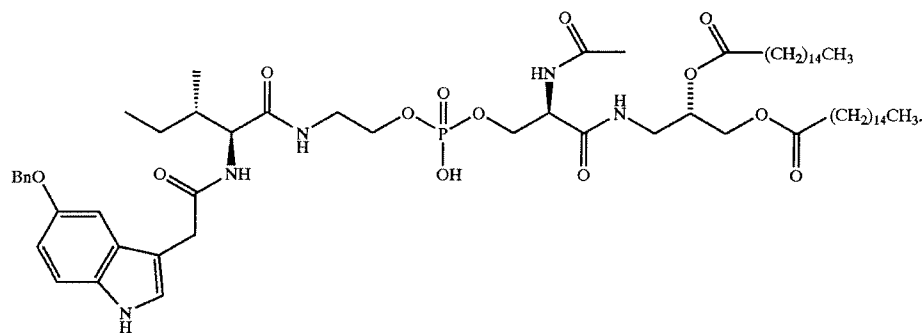
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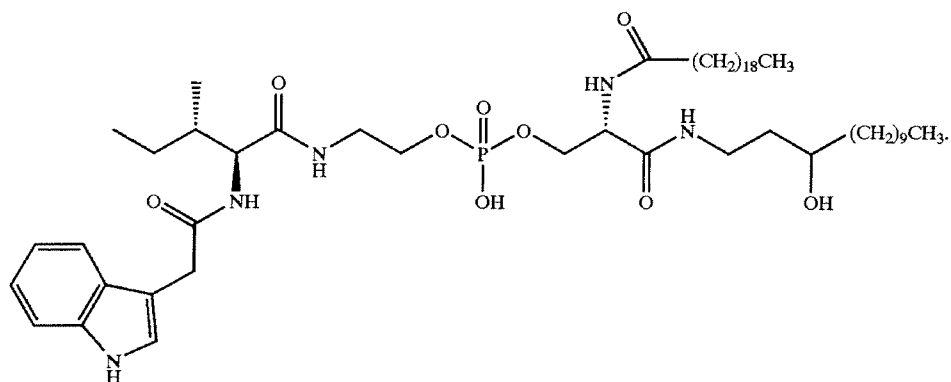
(XIII)



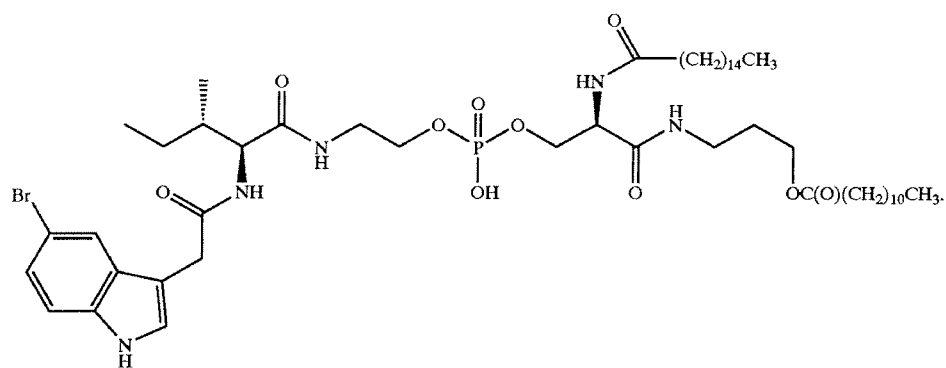
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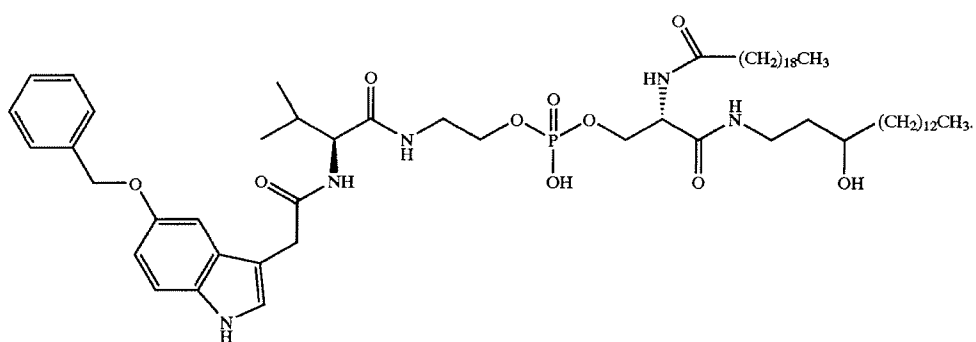
(XV)



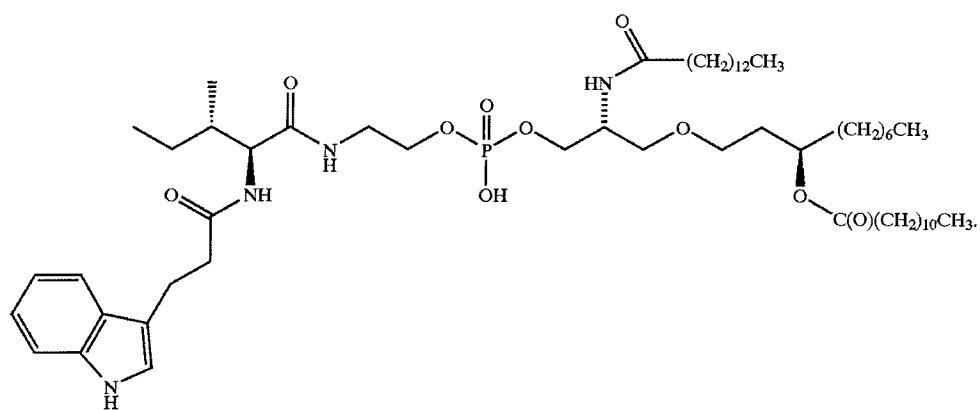
(XVI)



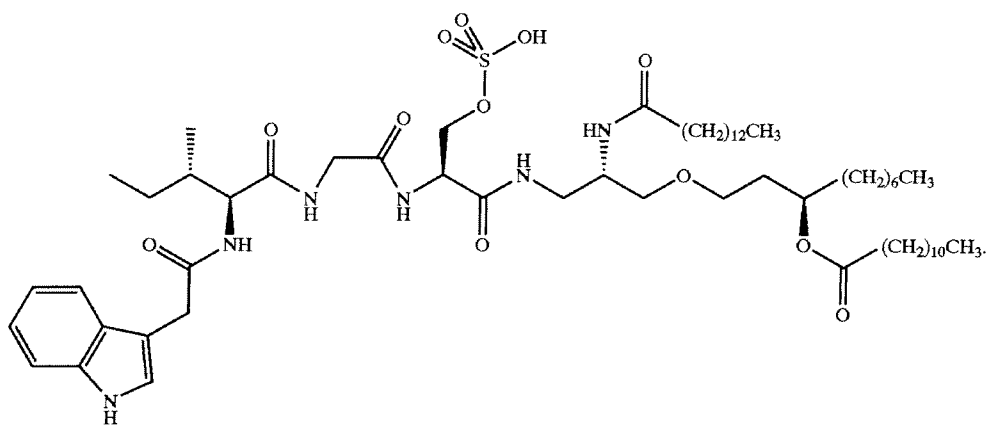
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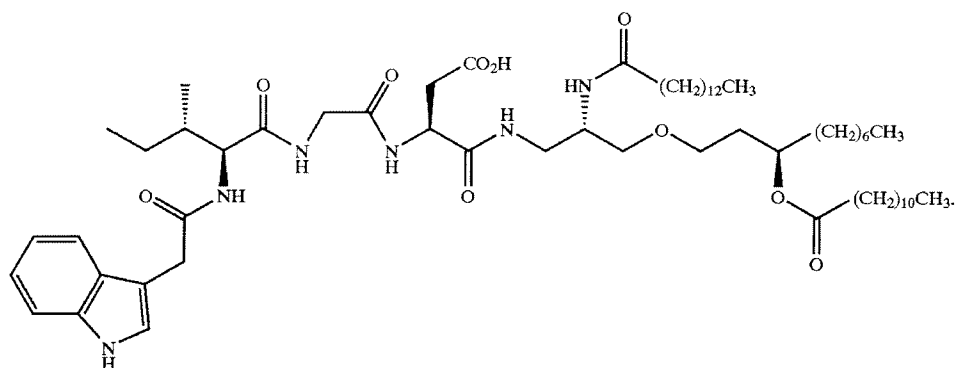
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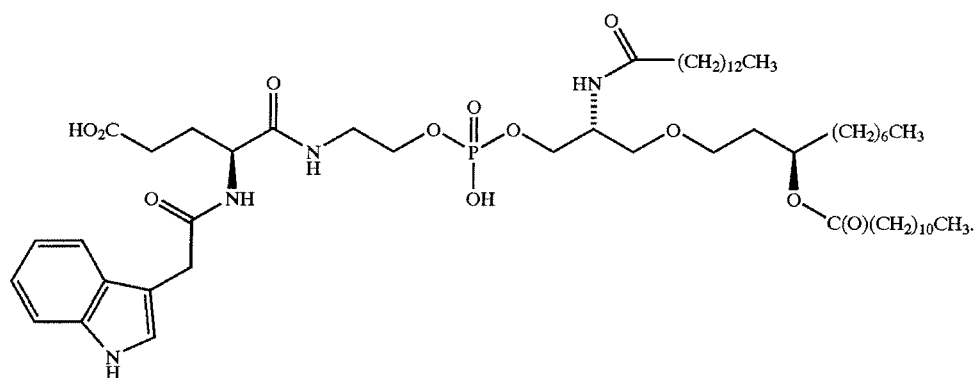
(XIX)



(XX)



(XXI)



(XXII)

wherein "Bn" represents the benzyl group.

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); YIHYSGYTDFNP SLKT (SEQ. NO. 16); KDPSDGFPY (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 other embodiments, a composition of the present invention comprises an antibody that binds to and inhibits the activity of TLR3. Non-limiting examples of

said antibodies have a heavy-chain CDR selected from the group consisting of SEQ. NO. 30 – 32 and a light-chain CDR selected from the group consisting of SEQ. NO. 33-35, as disclosed in U.S. Patent Application Publication 2006/0115475, which is incorporated herein by reference.

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 10 percent (from about 0.001 to about 5, 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.

An anti-infective agent suitable for a composition of the present invention is selected from the group consisting of antibacterial, antiviral, antifungal, antiprotozoal, and combinations thereof.

Non-limiting examples of biologically-derived antibacterial agents include aminoglycosides (e.g., amikacin, apramycin, arbekacin, bambermycins, butirosin, dibekacin, dihydrostreptomycin, fortimicin(s), gentamicin, isepamicin, kanamycin, micromonicin, neomycin, neomycin undecylenate, netilmicin, paromomycin, ribostamycin, sisomicin, spectinomycin, streptomycin, tobramycin, trospectomycin), amphenicols (e.g., azidamphenicol, chloramphenicol, florfenicol, thiamphenicol), ansamycins (e.g., rifamide, rifampin, rifamycin sv, rifapentine, rifaximin), β -lactams

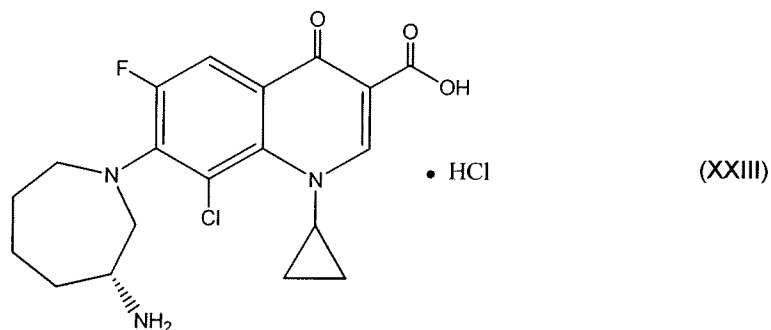
(e.g., carbacephems (e.g., loracarbef), carbapenems (e.g., biapenem, imipenem, meropenem, panipenem), cephalosporins (e.g., cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefcapene pivoxil, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefinenoxime, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotiam, cefozopran, cefpimizole, cefpiramide, cefpirome, cefpodoxime proxetil, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteram, ceftazole, ceftibuten, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephradine sodium, cephalixin, cephaloglycin, cephaloridine, cephalosporin, cephalothin, cephapirin sodium, cephradine, pivcefalexin), cephamycins (e.g., cefbuperazone, cefinetazole, cefininox, cefotetan, cefoxitin), monobactams (e.g., aztreonam, carumonam, tigemonam), oxacephems, flomoxef, moxalactam), penicillins (e.g., amdinocillin, amdinocillin pivoxil, amoxicillin, ampicillin, apalcillin, aspoxicillin, azidocillin, azlocillin, bacampicillin, benzylpenicillinic acid, benzylpenicillin sodium, carbenicillin, carindacillin, clometocillin, cloxacillin, cyclacillin, dicloxacillin, epicillin, fenbenicillin, floxacillin, hetacillin, lenampicillin, metampicillin, methicillin sodium, mezlocillin, nafcillin sodium, oxacillin, penamecillin, penethamate hydriodide, penicillin G benethamine, penicillin G benzathine, penicillin G benzhydrylamine, penicillin G calcium, penicillin G hydrabamine, penicillin G potassium, penicillin G procaine, penicillin N, penicillin O, penicillin V, penicillin V benzathine, penicillin V hydrabamine, penimepicycline, phenethicillin potassium, piperacillin, pivampicillin, propicillin, quinacillin, sulbenicillin, sultamicillin, talampicillin, temocillin, ticarcillin), ritipenem, lincosamides (e.g., clindamycin, lincomycin), macrolides (e.g., azithromycin, carbomycin, clarithromycin, dirithromycin, erythromycin, erythromycin acistrate, erythromycin estolate, erythromycin glucoheptonate, erythromycin lactobionate, erythromycin propionate, erythromycin stearate, josamycin, leucomycins, midecamycins, miokamycin, oleandomycin, primycin, rokitamycin, rosaramicin, roxithromycin, spiramycin, troleandomycin), polypeptides (e.g., amphomycin, bacitracin, capreomycin, colistin, enduracidin, enviomycin, fusafungine, gramicidin s, gramicidin(s), mikamycin, polymyxin, pristnamycin, ristocetin, teicoplanin, thiostrepton, tuberactinomycin, tyrocidine, tyrothricin, vancomycin, viomycin, virginiamycin, zinc bacitracin), tetracyclines (e.g., apicycline, chlortetracycline, clomocycline, demeclocycline, doxycycline, guamecycline, lymecycline, meclocycline, methacycline, minocycline,

oxytetracycline, penimepicycline, pipacycline, rolitetracycline, sancycline, tetracycline), cycloserine, mupirocin, and tuberin.

Non-limiting examples of synthetic antibacterial agents include 2,4-diaminopyrimidines (e.g., brodimoprim, tetroxoprim, trimethoprim), nitrofurans (e.g., furaltadone, furazolium chloride, nifuradene, nifuratel, nifurfoline, nifurpirinol, nifurprazine, nifurtinol, nitrofurantoin), quinolones and analogs (e.g., cinoxacin, ciprofloxacin, clinafloxacin, difloxacin, enoxacin, fleroxacin, flumequine, gatifloxacin, grepafloxacin, levofloxacin, lomefloxacin, miloxacin, moxifloxacin, nadifloxacin, nalidixic acid, norfloxacin, ofloxacin, oxolinic acid, pazufloxacin, pefloxacin, pipemidic acid, piromidic acid, rosoxacin, rifloxacin, sparfloxacin, temafloxacin, tosufloxacin, trovafloxacin, or a fluoroquinolone having the chemical name of 7-[(3R)-3-aminohexahydro-1H-azepin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid monohydrochloride), sulfonamides (e.g., acetyl sulfamethoxypyrazine, benzylsulfamide, chloramines B, chloramines T, dichloramine T, n^2 -formylsulfisomidine, n^4 - β -D-glucosylsulfanilamide, mafenide, 4'-(methylsulfamoyl)sulfanilamide, noprilsulfamide, phthalylsulfacetamide, phthalylsulfathiazole, salazosulfadimidine, succinylsulfathiazole, sulfabenzamide, sulfacetamide, sulfachlorpyridazine, sulfachrysoidine, sulfacytine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfadoxine, sulfaethidole, sulfaguanidine, sulfaguanol, sulfalene, sulfaloxic acid, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethomidine, sulfamethoxazole, sulfamethoxypyridazine, sulfametrole, sulfamidochrysoidine, sulfamoxole, sulfanilamide, 4-sulfanilamidosalicylic acid, n^4 -sulfanilylsulfanilamide, sulfanilylurea, N-sulfanilyl-3,4-xylamide, sulfanitran, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfasomizole, sulfasymazine, sulfathiazole, sulfathiourea, sulfatolamide, sulfisomidine, sulfisoxazole) sulfones (e.g., acedapsone, acediasulfone, acetosulfone sodium, dapsone, diathymosulfone, glucosulfone sodium, solasulfone, succisulfone, sulfanilic acid, p-sulfanilylbenzylamine, sulfoxone sodium, thiazolsulfone), clofoctol, hexedine, methenamine, methenamine anhydromethylene citrate, methenamine hippurate, methenamine mandelate, methenamine sulfosalicylate, nitroxoline, taurolidine, and xibomol. In one embodiment, a composition of the present invention comprises an anti-infective agent selected from the group consisting of cinoxacin, ciprofloxacin,

clinafloxacin, difloxacin, enoxacin, fleroxacin, flumequine, gatifloxacin, grepafloxacin, levofloxacin, lomefloxacin, miloxacin, moxifloxacin, nadifloxacin, nalidixic acid, norfloxacin, ofloxacin, oxolinic acid, pazufloxacin, pefloxacin, pipemidic acid, piromidic acid, rosoxacin, rufloxacin, sparfloxacin, temafloxacin, tosufloxacin, trovafloxacin, and the fluoroquinolones disclosed in U.S. Patents 5,385,900 and 5,447,926, which are incorporated herein by reference.

In one embodiment, an antibacterial agent included in a composition of the present invention comprises a fluoroquinolone having the chemical name of 7-[(3R)-3-aminohexahydro-1H-azepin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid monohydrochloride, having Formula XXIII.



Non-limiting examples of antiviral agents include Rifampin, Ribavirin, Pleconaryl, Cidofovir, Acyclovir, Pencyclovir, Gancyclovir, Valacyclovir, Famciclovir, Foscarnet, Vidarabine, Amantadine, Zanamivir, Oseltamivir, Resiquimod, antiproteases, PEGylated interferon (PegasysTM), anti HIV proteases (e.g. lopinivir, saquinivir, amprenavir, HIV fusion inhibitors, nucleotide HIV RT inhibitors (e.g., AZT, Lamivudine, Abacavir), non-nucleotide HIV RT inhibitors, Doconosol, interferons, butylated hydroxytoluene (BHT), and Hypericin.

Non-limiting examples of biologically-derived antifungal agents include polyenes (e.g., amphotericin B, candicidin, dermostatin, filipin, fungichromin, hachimycin, hamycin, lucensomycin, mepartricin, natamycin, nystatin, pecilocin, and perimycin), azaserine, griseofulvin, oligomycins, neomycin undecylenate, pyrrolnitrin, siccanin, tubercidin, and viridin.

Non-limiting examples of synthetic antifungal agents include allylamines (e.g., butenafine, naftifine, terbinafine), imidazoles (e.g., bifonazole, butoconazole, chlordantoin, chlormidazole, cloconazole, clotrimazole, econazole, enilconazole, fenticonazole, flutrimazole, isoconazole, ketoconazole, lanoconazole, miconazole, omoconazole, oxiconazole nitrate, sertaconazole, sulconazole, tioconazole), thiocarbamates (e.g., tolclate, tolindate, tolnaftate), triazoles (e.g., fluconazole, itraconazole, saperconazole, terconazole), acrisorcin, amorolfine, biphenamine, bromosalicylchloranilide, buclosamide, calcium propionate, chlorphenesin, ciclopirox, cloxyquin, coparaffinate, diamthazole dihydrochloride, exalamide, flucytosine, halethazole, hexetidine, loflucarban, nifuratel, potassium iodide, propionic acid, pyrrithione, salicylanilide, sodium propionate, sulbentine, tenonitroazole, triacetin, ujothion, undecylenic acid, and zinc propionate.

Non-limiting examples of antiprotozoal agents include polymycin B sulfate, bacitracin zinc, neomycin sulfate (e.g., Neosporin), imidazoles (e.g., clotrimazole, miconazole, ketoconazole), aromatic diamidines (e.g., propamidine isethionate, Brolene), polyhexamethylene biguanide ("PHMB"), chlorhexidine, pyrimethamine (Daraprim®), sulfadiazine, folic acid (leucovorin), clindamycin, and trimethoprim-sulfamethoxazole.

In one aspect, the anti-infective agent is selected from the group consisting of bacitracin zinc, chloramphenicol, ciprofloxacin hydrochloride, erythromycin, gatifloxacin, gentamicin sulfate, levofloxacin, moxifloxacin, ofloxacin, sulfacetamide sodium, polymyxin B, tobramycin sulfate, trifluridine, vidarabine, acyclovir, valacyclovir, famcyclovir, foscarnet, ganciclovir, formivirsen, cidofovir, amphotericin B, natamycin, fluconazole, itraconazole, ketoconazole, miconazole, polymyxin B sulfate, neomycin sulfate, clotrimazole, propamidine isethionate, polyhexamethylene biguanide, chlorhexidine, pyrimethamine, sulfadiazine, folic acid (leucovorin), clindamycin, trimethoprim-sulfamethoxazole, and combinations thereof.

The concentration of an anti-infective agent in a composition of the present invention can be in the range from about 0.001 to about 10 percent (from about 0.001 to about 5, 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.

In another aspect, a composition of the present invention can further comprise an additional medicament selected from the group consisting of immunosuppressants, cyclooxygenase-2 inhibitors, NSAIDs (non-steroidal anti-inflammatory drugs), DMARDS (disease-modifying anti-rheumatic drugs), antibiotics, 5-lipoxygenase inhibitors, LTB₄ antagonists, LTA₄ hydrolase inhibitors, anti-cell adhesion molecules (such as anti E-selectin), and combinations thereof.

In another aspect, a composition of the present invention further comprises an immunosuppressant. Non-limiting examples of immunosuppressants include cyclosporine, tacrolimus, rapamycin, azathioprine, 6-mercaptopurine, and combinations thereof.

Each of said additional medicaments, 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 can comprise a liquid medium. In one embodiment, the liquid medium comprises an aqueous solution.

In another aspect, a composition of the present invention can further comprise 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, and phenylethyl alcohol. 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, about 0.01 percent to about 2 percent by weight).

In one embodiment, a composition of the present invention comprises an anti-microbial 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]- α -[4-tris(2-hydroxyethyl)ammonio]-2-butenyl- ω -[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 reduce the microorganism population

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 by weight; preferably, from about 0.00003 to about 0.5 percent; and more preferably, from about 0.0003 to about 0.1 percent by weight.

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 by weight of the total composition. 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 ($-O-R-$) repeats 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 contents of these sections are incorporated herein by reference. 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 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 by weight, or 0.01 to 5 percent, or 0.01 to 2 percent, or 0.1 to 1.5 percent by weight.

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 by weight and preferably, from about 0.2 to about 1.5 percent by weight. 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 (2000rpm, 10 min) 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 20µg/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, MO) 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.

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 an infection of a tissue of an eye and sequelae thereof.

EXAMPLE 1:

Table 1

Ingredient	Amount (weight percent)
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
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
Compound having Formula XXIII	0.05
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 (weight percent)
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
Gatifloxacin	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 3:

Table 3

Ingredient	Amount (weight percent)
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
Moxifloxacin	0.06
Purified water	q.s. to 100

EXAMPLE 4:

Table 4

Ingredient	Amount (weight percent)
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
Compound having Formula XXIII	0.07
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 (weight percent)
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
Chloramphenicol	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 6:

Table 6

Ingredient	Amount (weight percent)
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
Miconazole	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 7:

Table 7

Ingredient	Amount (weight percent)
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
Acyclovir	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 8:

Table 8

Ingredient	Amount (weight percent)
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
Compound having Formula XXIII	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 9:

Table 9

Ingredient	Amount (weight percent)
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
ODN 2088	0.01
Clotrimazole	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 10:

Table 10

Ingredient	Amount (weight percent)
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
Compound having Formula XXIII	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 polyhexamethylenbiguanide 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 individual container that is opened and the contents of the container are used only once.

In another aspect, a composition of the present invention is formulated as an eye drop, which is applied in the ocular environment on a periodic basis (for example, daily, once every other day, weekly, bimonthly, or monthly) to provide a treatment or control of an infection of an eye and sequelae thereof. The present invention also provides a method for reducing risk of development, or severity, of an inappropriate immune response in an eye following an infection. The method comprises applying a composition to the eye, wherein the composition comprises: (a) 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; and (b) at least an anti-infective agent.

In another aspect, the concentration of 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 and the concentration of anti-infective agent in a composition of the present invention are in any one of the ranges disclosed herein for the respective active agents.

In still another aspect, the present invention provides a method for preparing a composition for the treatment or control of an ophthalmic infection and its sequelae in a subject. The method comprises combining: (a) 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; and (b) at least an anti-infective agent with a pharmaceutically acceptable carrier, diluent, excipient, additive, or combination thereof.

In one embodiment, a composition of the present invention is in 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 used to treat inflammation following infections.

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, 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, chlorprednisone, 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, formocortal, 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

Inhibitors of TLRs or TLR coreceptors 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 PARP inhibitor by measuring the activity of this enzyme. For example, in one procedure, the cells are treated for 24 hours with the test substance (a PARP inhibitor or glucocorticoid), and then the TAT activity is measured. The TAT activities for the selected PARP inhibitor 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 PARP inhibitor for the same condition.

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

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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: (a) 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; and (b) an anti-infective agent; wherein said antagonist, compound, or combination thereof, and said anti-infective agent are present at concentrations such that the composition is capable of treating or controlling an infection and sequelae thereof.
2. 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.
3. 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.
4. 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.
5. 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 microbe-expressed molecular structure.
6. 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.
7. The composition of claim 1, wherein said antagonist or said compound comprises an antibody of a TLR, wherein said antibody comprises a heavy-chain complementary determining region having an amino acid sequence selected from the group consisting of SEQ. NO. 9 – SEQ.NO. 20, SEQ. NO. 30 – 32, and combinations thereof.

8. The composition of claim 1, wherein said antagonist or said compound comprises an antibody of a TLR, wherein said antibody comprises a light-chain complimentary determining region having an amino acid sequence selected from the group consisting of SEQ. NO. 33 – SEQ.NO. 35 and combinations thereof
9. 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.
10. The composition of claim 1, wherein said antagonist or compound comprises a nucleotide sequence comprising multiple repeats of any one of SEQ. NO. 1 – SEQ. NO. 8, SEQ. NO. 21 – SEQ. NO. 29, and combinations thereof.
11. The composition of claim 10, 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.
12. 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.
13. The composition of claim 1, wherein said antagonist or compound comprises a ligand of vitamin D receptor.
14. The composition of claim 13, wherein said ligand of vitamin D receptor comprises vitamin D or an analogue thereof.
15. The composition of claim 13, wherein said ligand of vitamin D receptor comprises vitamin D₂, vitamin D₃, or a mixture thereof.
16. The composition of claim 1, wherein said antagonist or compound comprises a compound having one of Formulae I through XXII.

17. 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.
18. The composition of claim 4, wherein said antagonist or said compound is present in an amount in a range from about 0.001 to about 2 percent by weight of said composition.
19. The composition of claim 1, wherein said anti-infective agent is selected from the group consisting of antibacterial drugs, antifungal drugs, antiviral drugs, antiprotozoal drugs, and combinations thereof.
20. The composition of claim 1, wherein said anti-infective agent comprises a fluoroquinolone having Formula XXIII.
21. The composition of claim 1, wherein said anti-infective agent comprise moxifloxacin or gatifloxacin.
22. The composition of claim 1, further comprises a medicament selected from the group consisting of immunosuppressants, cyclooxygenase-2 inhibitors, NSAIDs (non-steroidal anti-inflammatory drugs), DMARDS (disease-modifying anti-rheumatic drugs), antibiotics, 5-lipoxygenase inhibitors, LTB₄ antagonists, LTA₄ hydrolase inhibitors, 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 19, further comprising a material selected from the group consisting of carriers, preservatives, antimicrobial agents, surfactants, buffers, tonicity-modifying agents, chelating agents, viscosity-modifying agents, co-solvents, oils, humectants, emollients, stabilizers, antioxidants, and combinations thereof.

25. The composition of claim 24, wherein the composition has a pH in a range from about 5 to about 8.
26. The composition of claim 24, wherein the composition has a pH in a range from about 6.5 to about 7.8.
27. 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) and a fluoroquinolone antibacterial; wherein the composition is capable of treating, reducing, ameliorating, alleviating, or preventing a dry eye condition; wherein 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 is present in an amount from about 0.0001 to about 5 percent by weight of said composition; said fluoroquinolone 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.
28. The composition of claim 27, wherein said fluoroquinolone comprises a compound having Formula XXIII.
29. The composition of claim 27, further comprises an additional medicament selected from the group consisting of immunosuppressants, cyclooxygenase-2 inhibitors, NSAIDs (non-steroidal anti-inflammatory drugs), DMARDS (disease-modifying anti-rheumatic drugs), antibiotics, 5-lipoxygenase inhibitors, LTB₄ antagonists, LTA₄ hydrolase inhibitors, 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.
30. A method for treating or controlling an infection and sequelae thereof in a subject, the method comprising administering to said subject a pharmaceutically effective amount of a composition that comprises: (a) 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; and (b) an anti-infective agent.

31. The method of claim 30; 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.

32. The method of claim 30, 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.

33. The method of claim 30, 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 microbe-expressed molecular structure, or a soluble form of CD14 or MD-2.

34. The method of claim 30, 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.

35. The method of claim 30, 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.

36. The method of claim 30, 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.

37. The method of claim 30, wherein said antagonist or said compound comprises a compound having one of Formulae I through XXII.

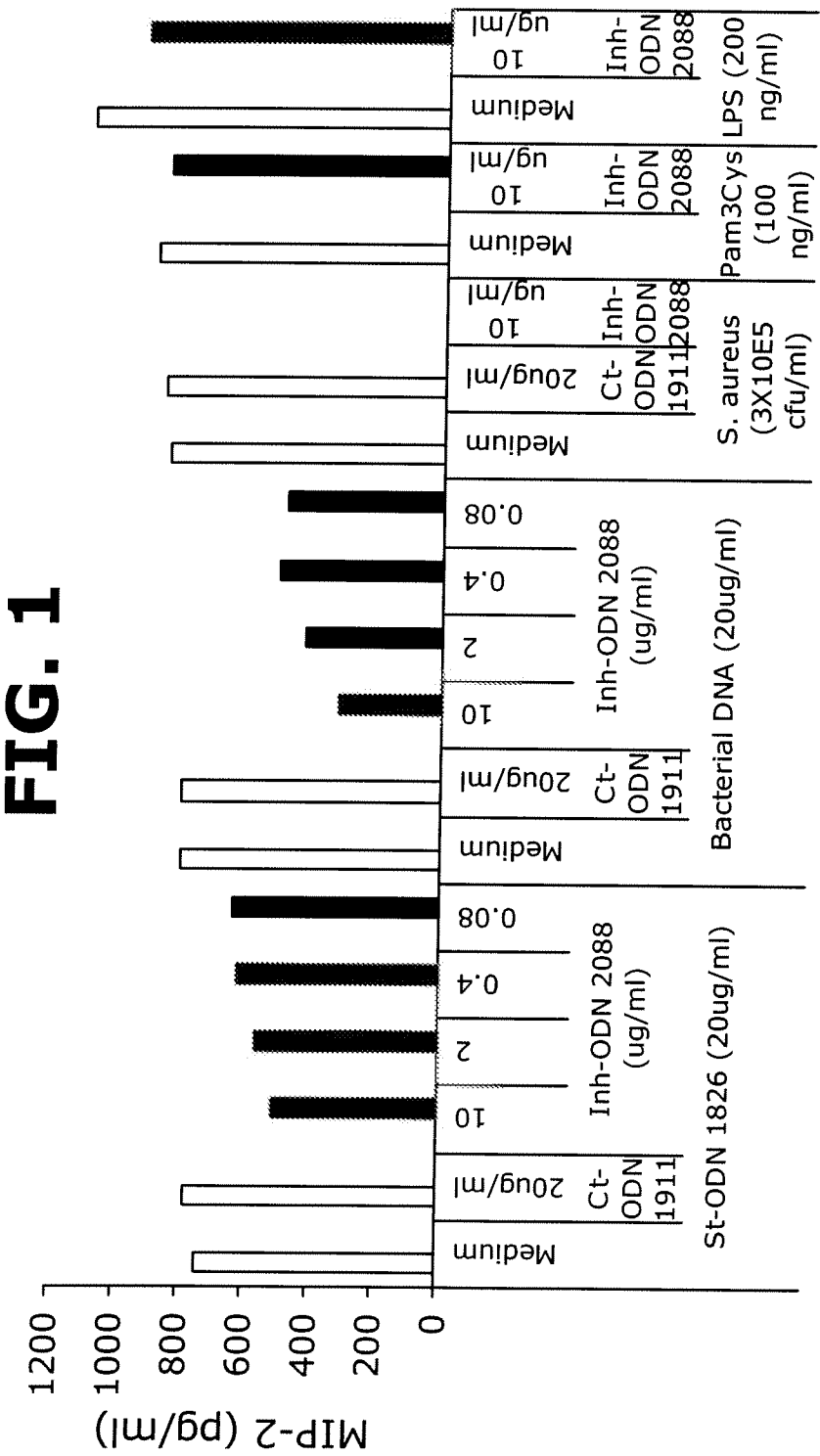
38. The method of claim 30, wherein said antagonist or said compound comprises an antibody of a TLR, wherein said antibody comprises a heavy-chain complimentary determining region having an amino acid sequence selected from the group consisting of SEQ. NO. 9 – SEQ. NO. 20, SEQ. NO. 30 – SEQ. NO. 32, and combinations thereof.
39. The method of claim 30, 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.
40. The method of claim 30, wherein said antagonist or compound comprises a ligand of vitamin D receptor.
41. The method of claim 40, wherein said ligand of vitamin D receptor comprises vitamin D or an analogue thereof.
42. The method of claim 40, wherein said ligand of vitamin D receptor comprises vitamin D₂, vitamin D₃, or a mixture thereof.
43. The method of claim 30, wherein said antagonist or said compound is present in an amount in a range from about 0.0001 to about 5 percent by weight, and said anti-infective agent is present in an amount in a range from about 0.0001 to about 5 percent by weight of said composition.
44. The method of claim 43, wherein said infection is an infection of an eye.
45. The method of claim 44, wherein said infection is selected from the group consisting of conjunctivitis, blepharitis, cellulitis, keratitis, corneal ulcer, trachoma, and combinations thereof.
46. The method of claim 30, wherein the composition further comprises an additional medicament selected from the group consisting of immunosuppressants, cyclooxygenase-2 inhibitors, NSAIDs (non-steroidal anti-inflammatory drugs), DMARDS (disease-modifying anti-rheumatic drugs), antibiotics, 5-lipoxygenase

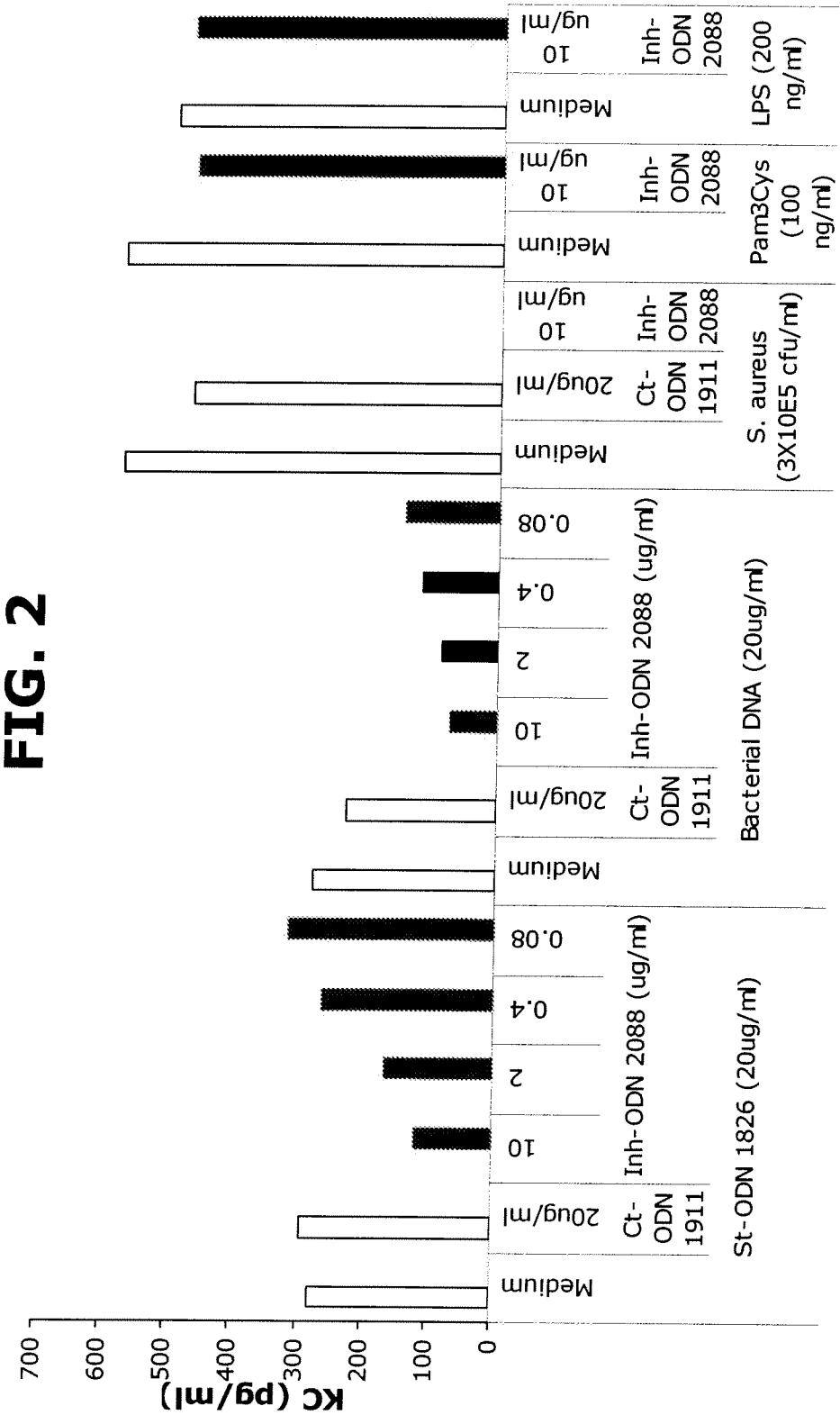
inhibitors, LTB₄ antagonists, LTA₄ hydrolase inhibitors, anti-cell adhesion molecules, and combinations thereof; wherein said additional medicament is present in an amount from about 0.0001 to about 5 weight percent.

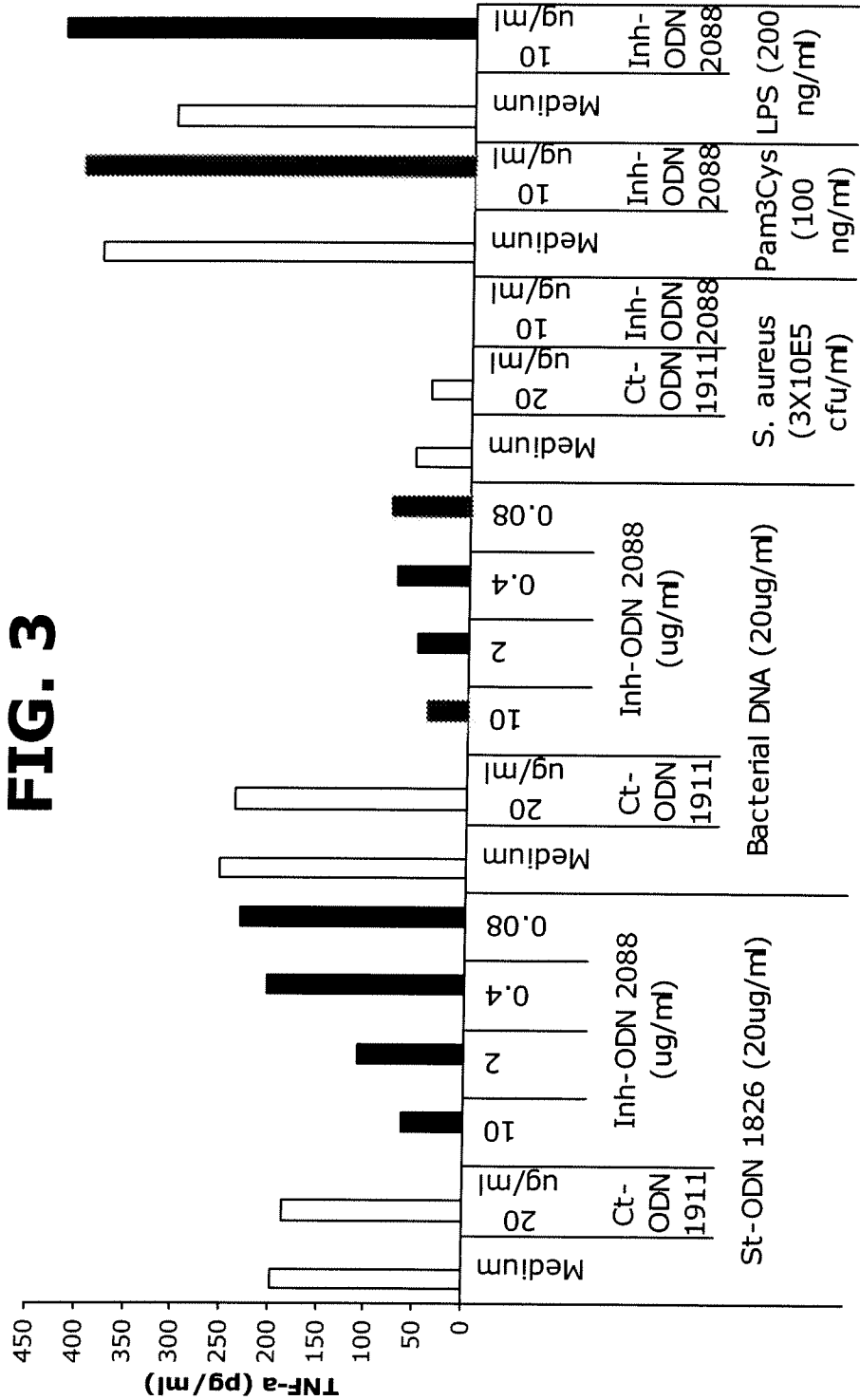
47. The method of claim 30, wherein said composition further comprises an immunosuppressant selected from the group consisting of cyclosporine, tacrolimus, rapamycinazathioprine, 6-mercaptopurine, and combinations thereof.

48. A method for preparing a composition for treating or controlling an infection and sequelae thereof in a subject, the method comprising combining: (a) 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; and (b) an anti-infective agent with a pharmaceutically acceptable carrier; wherein said antagonist, compound, or combination thereof and said anti-infective agent are present at concentrations such that the composition is capable of treating or controlling said infection and sequelae thereof in said subject.

49. The method of claim 48, further comprising adding a medicament selected from the group consisting of immunosuppressants, cyclooxygenase-2 inhibitors, NSAIDs (non-steroidal anti-inflammatory drugs), DMARDS (disease-modifying anti-rheumatic drugs), antibiotics, 5-lipoxygenase inhibitors, LTB₄ antagonists, LTA₄ hydrolase inhibitors, anti-cell adhesion molecules, and combinations thereof to the composition.







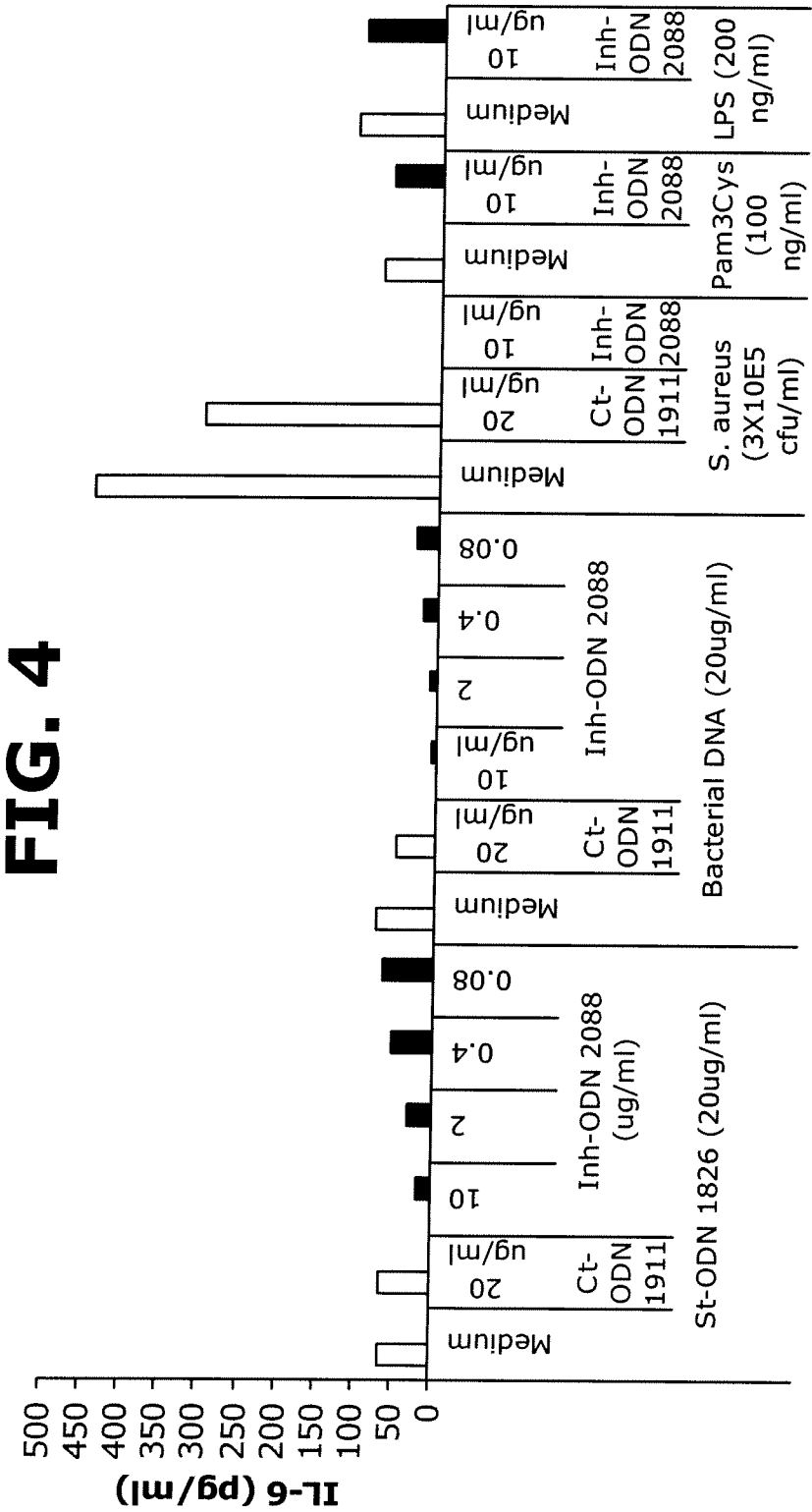


FIG. 5

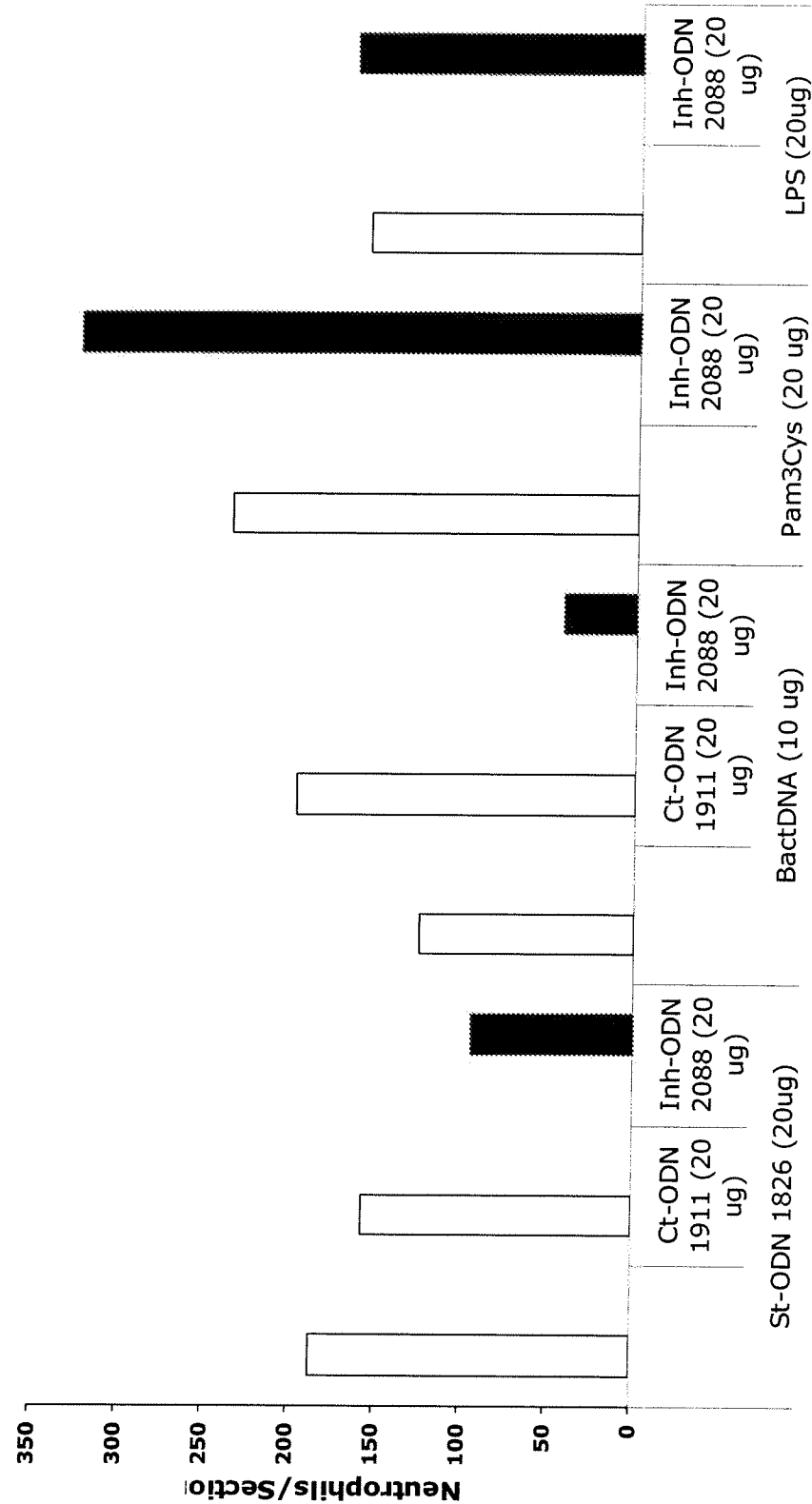


FIG. 6

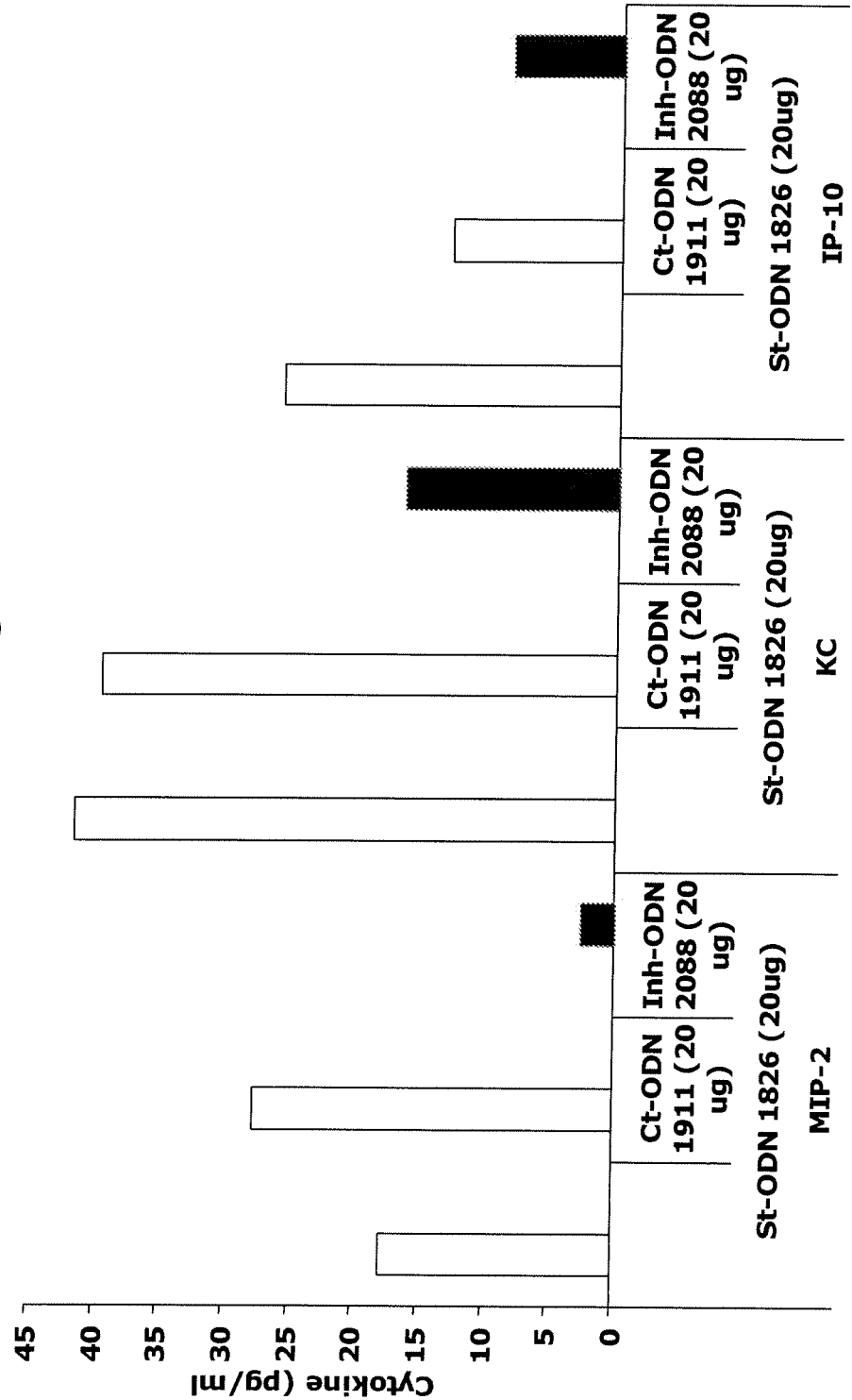


FIG. 7

