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(54) Title: COMPOSITIONS COMPRISING PKC-DELTA MODULATORS AND METHODS FOR OCULAR NEUROPRO-
TECTION

(57) Abstract: Compositions for treating or controlling degeneration of at least a component of the human optic nerve system
comprise a modulator of protein kinase Gdelta ('PKC-delta'). Such a PKC-delta modulator can be a compound that substantially
inhibits, reduces, or interferes with, an activity of a cell signaling cascade involving PKC-delta or activation of PKC-delta. The
compositions can also include an anti-inflammatory medicament. Such compositions can be administered to provide neuroprotec-
tion to a patient suffering from an ocular disease, such as glaucoma, AMD, DR, or retinitis pigmentosa.



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COMPOSITIONS COMPRISING PKC-DELTA MODULATORS AND METHODS FOR OCULAR NEUROPROTECTION

BACKGROUND

The present invention relates to compositions and methods for effecting ocular neuroprotection. In particular, the present invention relates to compositions that comprise modulators of protein kinase C- δ ("PKC- δ "), and to methods for effecting ocular neuroprotection using such compositions. In one aspect, the present invention relates to such compositions and methods for treating or controlling ocular neurodegenerative diseases.

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

Considering all types together, glaucoma occurs in about 2 percent of all persons over the age of 40 and may be asymptomatic for years before

progressing to rapid loss of vision. The underlying causes of primary glaucoma are not yet well known. An intraocular pressure ("IOP") that is high compared to the population mean is a risk factor for the development of glaucoma. However, many individuals with high IOP do not have glaucomatous loss of vision. Conversely, there are glaucoma patients with normal IOP. Therefore, continued efforts have been devoted to elucidate the pathogenic mechanisms of glaucomatous optic nerve degeneration.

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

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

meshwork ("TM") but also in retinal cells, appears to be involved in the neuronal cell death affecting the optic nerve in primary open-angle glaucoma ("POAG"). A. Izzotti et al., *Mutat. Res.*, Vol. 612, No. 2, 105 (2006).

In addition, tumor necrosis factor- α ("TNF- α "), a pro-inflammatory cytokine, has recently been identified to be a mediator of RGC death. TNF- α and TNF- α receptor-1 are up-regulated in experimental rat models of glaucoma. In vitro studies have further identified that TNF- α -mediated RGC death involves the activation of both receptor-mediated caspase cascade and mitochondria-mediated caspase-dependent and caspase-independent components of cell death cascade. G. Tezel and X. Yang, *Expt'l Eye Res.*, Vol. 81, 207 (2005). Moreover, TNF- α and its receptor were found in greater amounts in retina sections of glaucomatous eyes than in control eyes of age-matched normal donors. G. Tezel et al., *Invest. Ophthalmol. & Vis. Sci.*, Vol. 42, No. 8, 1787 (2001).

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

Retinitis pigmentosa, another back-of-the-eye disease, is the term for a group of inherited diseases that affect the retina, the delicate nerve tissue composed of several cell layers that line the inside of the back of the eye and contain photoreceptor cells. These diseases are characterized by a gradual breakdown and degeneration of the photoreceptor cells (the rod and cone cells), which result in a progressive loss of vision. Retinitis pigmentosa affects thousands of individuals in the United States. Together, rods and cones are the cells responsible for converting light into electrical impulses that transfer messages to the retinal ganglion cells which in turn transmit the impulses through the lateral geniculate nucleus into that area of the brain where sight is perceived. Retinitis pigmentosa, therefore, affects a different retinal cell type

than those affected by glaucoma. Depending on which type of photoreceptor cell is predominantly affected, the symptoms vary, and include night blindness, loss of peripheral vision (also referred to as tunnel vision), and loss of the ability to discriminate color before peripheral vision is diminished. Symptoms of retinitis pigmentosa are most often recognized in adolescents and young adults, with progression of the disease usually continuing throughout the patient's life. The rate of progression and degree of visual loss are variable. As yet, there is no known cure for retinitis pigmentosa.

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

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

the drusen grow as they accumulate inflammatory proteins and other materials, and the inflammation persists, causing additional damage to the retina and eventual vision loss. See; e.g., *Science*, Vol. 311, 1704 (2006).

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

Thus, it is now known that many serious back-of-the eye pathological conditions lead to loss of vision through progressive damage to various components of the optic nerve system. Consequently, current therapies attempt to prevent further damage to the remaining functioning cells of the optic nerve system. Pharmacological intervention with IOP-lowering drugs has been prescribed to slow or stop optic nerve degeneration resulting from glaucoma.

Recently, α_2 -adrenergic receptor agonists have been noted to have neuroprotective effect on RGCs. See; e.g., E. Wolde-Mussie et al., *Invest. Ophthalmol. & Vis. Sci.*, Vol. 42, No. 12, 2849 (2001); M.P. Lafuente Lopez-Herrera et al., *Expt'l Neurol.*, Vol. 178, 243 (2002). It has been reported that injected

brimonidine and clonidine, which are among the α_2 -adrenergic receptor agonists, delay the secondary degeneration of axons after a partial optic nerve crush in rats, and the neuroprotective effect could be blocked by α_2 -antagonists. A.T.E. Hartwick, *Optometry and Vision Science*, Vol. 78, No. 2, 85 (2001) (noting E. Yoles et al., *Ophthalmol. Vis. Sci.*, Vol. 40, 65 (1999)).

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

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

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

SUMMARY

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

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

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

In still another aspect, a composition of the present invention comprises a modulator of PKC- δ , in an effective amount for treating or controlling degeneration of at least a component of the human optic nerve system.

In yet another aspect, a composition of the present invention comprises a compound that substantially inhibits, reduces, or interferes with, an activity of a cell signaling cascade involving PKC- δ , in an effective amount for treating or controlling degeneration of at least a component of the human optic nerve system.

In yet another aspect, a composition of the present invention comprises an inhibitor of, or an antagonist to, PKC- δ , or an inhibitor of activation of PKC- δ , in an amount effective for treating or controlling degeneration of at least a component of a human optic nerve system in a subject. A compound that substantially inhibits, reduces, or interferes with, an activity of a cell signaling cascade involving PKC- δ , antagonizes PKC- δ , or inhibits the activation of PKC- δ hereinafter sometimes referred to as “PKC- δ inhibitor.”

In still another aspect, such PKC- δ is a human PKC- δ .

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

In yet another aspect, such PKC- δ is activated in a cell or tissue associated with the human optic nerve system.

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

In still another aspect, such a PKC- δ inhibitor is capable of down regulating a cell signaling pathway involving PKC- δ .

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

In a further aspect, a composition of the present invention comprises: (a) a PKC- δ inhibitor; and (b) an anti-inflammatory medicament.

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

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

DETAILED DESCRIPTION

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

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

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

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

In one aspect, a pharmaceutical composition of the present invention comprises an inhibitor of an activity of, or an antagonist to, PKC- δ , or an inhibitor of activation of PKC- δ , in an amount effective for providing neuroprotection to cells or components of a nervous system.

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

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

As used herein, the term “PKC- δ inhibitor” also includes compounds that inhibit or impede the expression or activation of PKC- δ . In one embodiment, such PKC- δ inhibitor inhibits or is present in the composition at concentrations such that the composition is capable of treating or controlling neurodegeneration in a subject.

In another aspect, such PKC- δ is human PKC- δ .

In still another aspect, such a PKC- δ inhibitor is capable of down regulating a cell signaling pathway involving PKC- δ .

In still another aspect, such PKC- δ is over-expressed in a cell or tissue associated with the human optic nerve system.

In still another aspect, such PKC- δ is over-activated in a cell or tissue associated with the human optic nerve system.

Chronic stress imposed on cells, including those of the nervous system, can lead to their degeneration and, eventually, death if such stress is not relieved promptly. Such degeneration usually begins with dysregulation of one or more biological compounds that are key to the maintenance of homeostasis.

The protein kinase C (“PKC”) family comprises twelve closely related isoforms of serine/threonine kinases. The PKC family is subdivided into three

major groups. The conventional PKCs include the α , β I, β II, and γ isoforms and are activated by Ca^{2+} and diacylglycerol (“DAG”), a level of which can increase because of hyperglycemia or diabetic state. The novel PKCs include the δ , ϵ , η , and θ isoforms and are activated by DAG, but not Ca^{2+} . The atypical PKCs include the ζ and λ/ι isoforms, which are insensitive to both Ca^{2+} and DAG. PKC isoenzymes play a pivotal role as cellular mediators of signal transduction for hormones and growth factors as well as regulating diverse processes, including vascular haemodynamics, cellular proliferation and migration, neovascularization, enzyme activities, and gene expression of both growth factors and proto-oncogenes. Thus, amounts of PKC proteins are found in most types of tissues at regulated levels for normal body function. However, some PKC isozymes show distinctive distribution in different tissues. For example, PKC- β I and - β II are present in greatest amount in the brain and spleen. PKC- γ is seen mostly in the brain, and to a lesser degree, in the adrenal tissue. PKC- δ is concentrated in the brain, heart, spleen, lung, liver, ovary, pancreas, and adrenal tissues. PKC- ϵ is present in the brain, kidney, and pancreas. PKC- ζ is found mostly in the brain, lung, and liver. PKC- θ is present predominantly in T lymphocytes and muscle cells. In particular, PKC- δ is only one of three PKCs (along with PKC- α and PKC- β II) found in retinal pigment epithelial (“RPE”) cells, pericytes, and endothelial cells of the retina.

With respect to the central nervous system (“CNS”), there is substantial evidence that PKC- δ promotes the programmed cell death (apoptosis) of hippocampal nerve cells induced by oxidative stress. P. Maher, *J. Neurosci.*, Vol. 21, No. 9, 2929 (2001). It was shown that activation of PKC- δ is essential for oxidative stress-mediated death of dopaminergic neurons after exposure to methylcyclopentadienyl manganese tricarbonyl, a neurotoxicant that induces reactive oxygen species (“ROS”) generation and dopamine depletion, in a caspase-3 dependent manner. Continuing death of dopaminergic neurons has

been attributed to the progression of Parkinson's disease. V. Anantharam et al., *J. Neurosci.*, Vol. 22, No. 5, 1738 (2002).

Other related evidence indicates that neutrophils PKC- δ and neuronal PKC- δ contribute to the development of stroke reperfusion injury. Neutrophil PKC- δ appears to play a major role in regulating the release of superoxide anion. PKC- δ also promotes neutrophils degranulation, facilitating the release of proteases that can damage the brain tissues. Reperfusion events also increase levels of DAG in neuronal cells, which can activate PKC- δ in these cells. W.H. Chou and R.O. Messing, *Trends Cardiovasc. Med.*, Vol. 15, 47 (2005). The present inventors recognize that such results can occur similarly in optic nerve tissues following retinal ischemia resulting from a prolonged diabetic state.

In addition, PKC- δ becomes activated during glutamate-induced oxidative stress. Prolonged glutamate-induced activation of PKC- δ leads to reduced activity of mitogen-activated kinase phosphatase-1 ("MKP-1"), which regulates cell survival, differentiation, and apoptosis, and eventually neuronal cell death. B-H Choi et al., *J. Cell Sci.*, Vol. 119, No.7, 1329 (2005). Glutamate is the principal excitatory neurotransmitter in the CNS, including retinal ganglion cells, and is normally released from presynaptic terminals of neurons in controlled small amounts. After binding to glutamate receptors, glutamate is taken up by excitatory amino-acid transporters mainly into glia where it is metabolized to glutamine. This uptake is the primary mechanism for extracellular glutamate clearance to protect the CNS from glutamate excitotoxicity. However, excessive or prolonged glutamate release following extended exposure to stimuli or stress and/or impairment of glutamate uptake and the resulting excessive stimulation of glutamate receptors have been implicated in neuronal death associated with a wide range of neurodegenerative diseases, such as Parkinson's disease, Huntington's disease, and Alzheimer's disease. B-H Choi et al., *supra*. Glutamate is released in large amounts by neurons following ischemic insults. Chronic

elevation of glutamate level was shown to be toxic to retinal ganglion cells. C.K. Vorwerk et al., *Invest. Ophthalmol. Vis. Sci.*, Vol. 37, No. 8, 1618 (1996).

In another aspect, the level of glutamate in retina of diabetic rats was found to increase by 40 folds. R.A. Kowluru et al., *Neurochem. Int'l*, Vol. 38, 385 (2001). In addition, glutamate was found to accumulate in the vitreous of diabetic patients with proliferative diabetic retinopathy. J. Ambati et al., *Arch. Ophthalmol.*, Vol. 115, 1161 (1997). Further, it was shown that an acute partial lesion of the optic nerve in a rat model as a simulated condition of glaucomatous injury led to intraocular elevation of glutamate by 54%, three days, and 79%, seven days after the onset of the injury. E. Yoles et al., *Arch. Ophthalmol.*, Vol. 116, 906 (1998). The present inventors recognize that prolonged excitation by glutamate leads to activation of PKC- δ and eventually, neuronal death, and thus, inhibition of PKC- δ activity can provide ocular neuroprotection to patient having ocular neurodegenerative conditions resulting from diabetes, such as diabetic retinopathy. However, the role of PKC δ in the ocular neuropathology has not been found in, or suggested by, the prior art, explicitly or by inference.

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

In another aspect, such compositions provide ocular neuroprotection in the subject through inhibiting or antagonizing activity of human PKC- δ .

In still another aspect, a composition of the present invention comprises a modulator of PKC- δ , in an effective amount for treating or controlling degeneration of at least a component of the human optic nerve system.

In yet another aspect, a composition of the present invention comprises a compound that substantially inhibits, reduces, or interferes with, an activity of a cell signaling cascade involving PKC- δ , in an effective amount for treating or controlling degeneration of at least a component of the human optic nerve system.

In a further aspect, a composition of the present invention comprises a compound that substantially inhibits, reduces, or interferes with, activation of PKC- δ , in an effective amount for treating or controlling degeneration of at least a component of the human optic nerve system.

In yet another aspect, a composition of the present invention comprises a PKC- δ inhibitor and an anti-inflammatory medicament. Preferably, such an anti-inflammatory medicament comprises a nonsteroidal compound.

The sequences of DNA encoding human PKC- δ (SEQ. NO. 1) and of human PKC- δ protein (SEQ. NO. 2) are shown in the Sequence Listing below. PKC- δ protein comprises a regulatory domain and a catalytic domain. The regulatory domain (including amino acids 1-280) comprises a subdomain C1 homologous to other members of the PKC family and three variable subdomains V1, V2, and V3. The catalytic domain (including amino acids 349-675) comprises homologous subdomains C3 and C4 and variable domains V4 and V5.

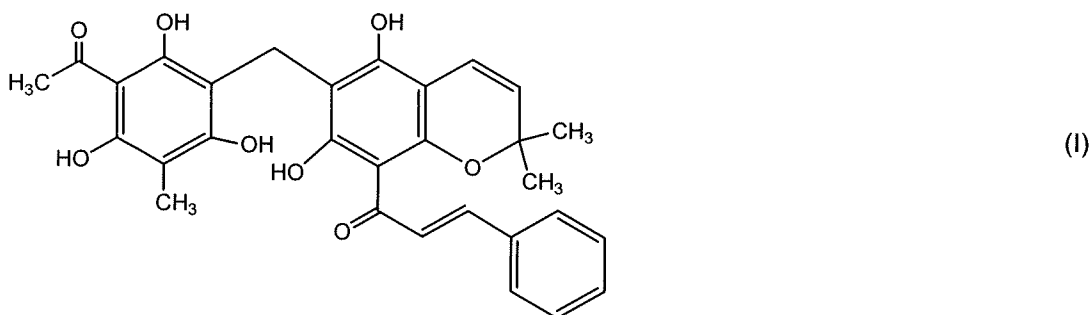
In one aspect, a PKC- δ inhibitor comprises an agent which decreases the level of PKC- δ expression and/or activity. An agent that decreases the level of PKC- δ expression or activity can be one or more of: a PKC- δ antagonist (e.g., a PKC- δ binding protein that binds to PKC- δ but does not activate the enzyme); a PKC- δ nucleic acid molecule that can bind to a cellular PKC- δ nucleic acid sequence (e.g., mRNA) and inhibit expression of the protein (e.g., an antisense molecule or PKC- δ ribozyme); an antibody that specifically binds to PKC- δ protein

(e.g., an antibody that disrupts PKC- δ 's catalytic activity or an antibody that disrupts the ability of upstream activators to activate PKC- δ); an agent that decreases PKC- δ gene expression and/or activity (e.g., a small molecule that inhibits PKC- δ (e.g., Rottlerin, disclosed below)).

In another aspect, PKC- δ expression is inhibited by decreasing the level of expression of an endogenous PKC- δ gene (e.g., by decreasing transcription of the PKC- δ gene). In one embodiment, transcription of the PKC- δ gene can be decreased by: altering the regulatory sequences of the endogenous PKC- δ gene (e.g., by the addition of a negative regulatory sequence, such as a DNA-binding site for a transcriptional repressor, or by the removal of a positive regulatory sequence, such as an enhancer or a DNA-binding site for a transcriptional activator).

Small-Molecule PKC- δ Inhibitors

In another aspect, a PKC- δ inhibitor included in a composition of the present invention comprise rottlerin (also known as mallotoxin or 1-[6-[(3-acetyl-2,4,6-trihydroxy-5-methylphenyl)methyl]-5,7-dihydroxy-2,2-dimethyl-2H-1-benzopyran-8-yl]-3-phenyl-2-propen-1-one, available from Calbiochem, San Diego, California) having Formula I, or a derivative or analogue thereof.



Antibodies

In another aspect, a PKC- δ inhibitor included in a composition of the present invention comprises an antibody specifically reactive with human PKC- δ or a fragment of such antibody.

Anti-protein/anti-peptide antisera or monoclonal antibodies can be made by using standard protocols (See; e.g., *"Antibodies: A Laboratory Manual"* ed. by Harlow and Lane (Cold Spring Harbor Press, 1988)).

PKC- δ , or a portion or fragment thereof, can be used as an immunogen to generate antibodies that bind the component using standard techniques for polyclonal and monoclonal antibody preparation. The full-length protein can be used or, alternatively, antigenic peptide fragments of the protein can be used as immunogens.

Typically, a peptide is used to prepare antibodies by immunizing a suitable subject (e.g., rabbit, goat, mouse or other mammal) with the immunogen. An appropriate immunogenic preparation can contain, for example, a recombinant or a chemically synthesized PKC peptide. See, e.g., US Patents 5,460,959; 5,994,127; 6,048,729; and 6,063,630; which are hereby expressly incorporated by reference in their entirety. The nucleotide and amino acid sequence of human PKC- δ is shown below (SEQ. NO.1). The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or similar immunostimulatory agent. Immunization of a suitable subject with an immunogenic PKC- δ preparation induces a polyclonal anti-PKC antibody response.

Fragments of antibodies to PKC- δ , such as Fv, Fab, Fab' and F(ab')₂ fragments, can be generated by treating the antibody with an enzyme such as

pepsin. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope. A monoclonal antibody composition thus typically displays a single binding affinity for a particular protein with which it immunoreacts.

In addition, antibodies produced by genetic engineering methods, such as chimeric or humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, can be used. Such chimeric or humanized monoclonal antibodies can be produced by genetic engineering using standard DNA techniques known in the art, for example using methods described in US Patents 5,721, 108; 5,677,180 and 5,50,362 (Robinson et al.); US Patent 4,935,496 (Akira et al.); US Patent 5,807,715 (Morrison et al.); US Patent 4,816,567 (Cabilly et al.); which are incorporated herein by reference in their entirety; A.Y. Liu et al., *PNAS*, Vol. 84, No. 10, 3439 (1987); L.K. Sun et al., *PNAS*, Vol. 84, No. 1, 214 (1987); Y. Nishimura et al., *Canc. Res.*, Vol. 47, 999 (1987).

In addition, a monoclonal antibody directed against human PKC- δ described herein can be made using standard techniques. For example, monoclonal antibodies can be generated in transgenic mice or in immune deficient mice engrafted with antibody-producing human cells. Methods of generating such mice are describe, for example, in S.L. Morrison et al., *PNAS*, Vol. 81, No. 21, 6851 (1984); N. Tuaillon et al., *PNAS*, Vol. 90, No.8, 3720 (1993); US Patent 5,411,749. A human antibody-transgenic mouse or an immune deficient mouse engrafted with human antibody-producing cells or tissue can be immunized with human PKC- δ isoform described herein or an antigenic peptide thereof and splenocytes from these immunized mice can then be used to create hybridomas. Methods of hybridoma production are well known. Antibodies

produced from such transgenic animal have been known to be well tolerated in human.

Monoclonal antibodies against human PKC- δ isoform disclosed herein can also be prepared by constructing a combinatorial immunoglobulin library, such as a Fab phage display library or a scFv phage display library, using immunoglobulin light chain and heavy chain cDNAs prepared from mRNA derived from lymphocytes of a subject. See, e.g., US Patent 5,969,108 (McCafferty et al.), which is incorporated herein by reference in its entirety, and A.D. Griffiths et al., *EMBO J*, Vol. 12, No. 2, 725 (1993). In addition, a combinatorial library of antibody variable regions can be generated by mutating a known human antibody. For example, a variable region of a human antibody known to bind PKC- δ can be mutated by, for example, using randomly altered mutagenized oligonucleotides, to generate a library of mutated variable regions which can then be screened to bind to PKC- δ . Methods of inducing random mutagenesis within the CDR regions of immunoglobulin heavy and/or light chains, methods of crossing randomized heavy and light chains to form pairings and screening methods can be found in, for example, US Patent 5,667,988 (Barbas III et al.), which is incorporated herein by reference in its entirety, and C.F. Barbas III et al., *PNAS*, Vol. 89, No. 10, 4457 (1992).

The immunoglobulin library can be expressed by a population of display packages, preferably derived from filamentous phage, to form an antibody display library. Non-limiting examples of methods and reagents particularly amenable for use in generating antibody display library can be found in, for example, US Patent 5,223,409 (Ladner et al.); US Patent 5,759,817 (Kang et al.); and US Patent 5,969,108 (McCafferty et al.); which are incorporated herein by reference in their entirety; A.D. Griffiths et al. (1993) *supra*; H. Gram et al., *PNAS*, Vol. 89, No. 8, 3576 (1992); and C.F. Barbas III et al., *PNAS*, Vol. 88, No. 18,

7978 (1991). Once displayed on the surface of a display package (e.g., filamentous phage), the antibody library is screened to identify and isolate packages that express an antibody that binds PKC- δ described herein. In one embodiment, the primary screening of the library involves panning with an immobilized PKC- δ described herein and display packages expressing antibodies that bind the immobilized PKC- δ are selected.

In another aspect, antibodies to human PKC- δ may be obtained from Santa Cruz Biotechnology, Inc., Santa Cruz, California; Calbiochem, San Diego, California; or Abcam Inc., Cambridge, Massachusetts (e.g. SEQ. NO. 7-8).

Short Peptide PKC- δ Antagonists

In still another aspect, a PKC- δ inhibitor included in a composition of the present invention comprises a short peptide PKC- δ antagonist having a sequence selected from the group consisting of SEQ. NO. 9-42. These short peptides can be recombinantly produced or chemically synthesized. The peptides having SEQ. NO. 9-42 and other suitable related short peptides are disclosed in US Patent 6,855,693; which is incorporated herein by reference in its entirety.

Antisense Nucleic Acid Sequences

Targeted inhibition of gene expression has become a fruitful approach for therapeutic intervention of diseases. Nucleic acid molecules that are "antisense" to a nucleotide sequence encoding human PKC- δ can be used as an agent that inhibits expression of human PKC- δ . An "antisense" nucleic acid includes a nucleotide sequence that is complementary to a "sense" nucleic acid encoding the protein, e.g., complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence. Accordingly, an antisense nucleic acid can form hydrogen bonds with a sense nucleic acid. The

antisense nucleic acid can be complementary to an entire coding strand, or to only a portion thereof. For example, an antisense nucleic acid molecule that is complementary to the “coding region” of the coding strand of a nucleotide sequence encoding the protein can be used.

The nucleic acid sequence encoding human PKC- δ (SEQ. NO. 1) is shown in the Sequence Listing below. Given the coding sequence encoding the isozyme, an antisense nucleic acid can be designed according to the rules of Watson and Crick base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of mRNA, but more preferably is an oligonucleotide which is antisense to only a portion of the coding or noncoding region of mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of the mRNA. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (e.g., an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil,

beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocyto sine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (i.e., RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest.

RNA-Interfering PKC- δ Inhibitors

In another aspect, a PKC- δ inhibitor included in a composition of the present invention comprises a small nucleic acid molecule that downregulates, inhibits, or reduces the expression of PKC- δ , or the expression or activity of another gene involved in a pathway of PKC- δ gene expression. Non-limiting examples of such nucleic acid molecules include short interfering nucleic acid ("siNA"), short interfering RNA ("siRNA"), double stranded RNA ("dsRNA"), micro-RNA ("miRNA"), and short hairpin RNA ("shRNA"). Techniques for making these nucleic acid molecules are disclosed, for example, in US Patents 5,514,567; 5,561,222; 6,506,559; 7,022,828; 7,078,196; 7,176,304; 7,282,564; and 7,294,504; which are incorporated herein by reference in their entirety. In one aspect, such an interfering RNA can be readily designed when the nucleic acid sequence for the target is known.

Alternatively, useful PKC- δ siRNAs may be those available from Addgene, Inc., Cambridge, Massachusetts, or from Qiagen, Inc., Valencia, California.

In other embodiments, a PKC- δ inhibitor that may be included in compositions of the present invention comprises a plasmid comprising a nucleic acid sequence, such as those selected from the group consisting of SEQ. NO. 3-4, ligated to a vector, such as pSUPER, for expressing siRNA. P. Storz et al., *Mol. Cell. Biol.*, Vol. 24, 2614 (2004). pSUPER vector is available from OligoEngine, Seattle, Washington. See also T. R. Brummelkamp et al., *Cancer Cell*, Vol. 2, 243 (2002). Alternatively, another vector, such as the pLTR vector (available from Addgene, Inc., Cambridge, Massachusetts) also can be used. Alternatively, the vector can be an adenovirus vector, available from, for example, Quantum Biotechnologies, Inc., Laval, Quebec, Canada.

In a further embodiment, an RNA-interfering PKC- δ inhibitor can be a naked nucleic acid having SEQ. NO. 5-6. N. Irie et al., *Biochem Biophys. Res. Comm.*, Vol. 298, 738 (2002).

Methods of introducing a nucleic acid molecule into a cell are disclosed herein below.

In yet another aspect, a PKC- δ inhibitor 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 PKC- δ inhibitor 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 0.01 to about 1, or from about 0.001 to about 0.01, or from about 0.001 to about 0.1 percent, or from about 0.1 to about 5, or from about 0.1 to about 2, or from about 0.1 to about 1, or from about 0.1 to about 0.5, or from about 0.1 to about 0.2) by weight of the composition.

In another aspect, a composition of the present invention comprises: (a) a PKC- δ inhibitor; and (b) an anti-inflammatory agent.

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

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

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

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

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

choriocapillaris, uveal tract, conjunctival epidermis, and intraocular muscles (see, e.g., U.S. Patent 6,316,465).

In one aspect, a PPAR γ agonist used in a composition or a method of the present invention is a thiazolidinedione, a derivative thereof, or an analog thereof. Non-limiting examples of thiazolidinedione-based PPAR γ agonists include pioglitazone, troglitazone, ciglitazone, englitazone, rosiglitazone, and chemical derivatives thereof. Other PPAR γ agonists include Clofibrate (ethyl 2-(4-chlorophenoxy)-2-methylpropionate), clofibric acid (2-(4-chlorophenoxy)-2-methylpropanoic acid), GW 1929 (N-(2-benzoylphenyl)-O-{2-(methyl-2-pyridinylamino)ethyl}-L-tyrosine), GW 7647 (2-{{4-{2-{{(cyclohexylamino)carbonyl}(4-cyclohexylbutyl)amino}ethyl}}phenyl}thio}-2-methylpropanoic acid), and WY 14643 ({{4-chloro-6-{{(2,3-dimethylphenyl)amino}-2-pyrimidinyl}thio}acetic acid). GW 1929, GW 7647, and WY 14643 are commercially available, for example, from Koma Biotechnology, Inc. (Seoul, Korea). In one embodiment, the PPAR γ agonist is 15-deoxy- Δ -12, 14-PG J2.

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

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

Other Suitable Ingredients in a Composition of the Present Invention

In one aspect, in addition to a PKC- δ inhibitor, a composition of the present invention comprises a liquid medium. In one embodiment, the liquid medium comprises an aqueous solution. In another aspect, the liquid medium comprises a non-aqueous formulation.

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

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

In one embodiment, a composition of the present invention comprises an 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], [4-tris(2-hydroxyethyl)ammonio]-2-butenyl-w-[tris(2-hydroxyethyl)ammonio]dichloride (chemical registry number 75345-27-6) generally available as Polyquaternium-1[®] from ONYX Corporation.

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

In one aspect, a composition of the present invention includes a disinfecting amount of an antimicrobial agent that will at least prevent the growth of microorganisms in the formulations employed. Preferably, a disinfecting amount is that which will reduce the microbial burden by two log orders in four hours and more preferably by one log order in one hour. Typically, such agents are present in concentrations ranging from about 0.00001 to about 0.5 percent (w/v); preferably, from about 0.00003 to about 0.5 percent (w/v); and more preferably, from about 0.0003 to about 0.1 percent (w/v).

In another aspect, a composition of the present invention comprises a surfactant. Suitable surfactants can be amphoteric, cationic, anionic, or non-ionic, which may be present (individually or in combination) in amounts up to 15 percent, preferably up to 5 percent weight by volume (w/v) of the total composition (solution). In one embodiment, the surfactant is an amphoteric or non-ionic surfactant, which when used imparts cleaning and conditioning properties. The surfactant should be soluble in the lens care solution and non-

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

Various other ionic as well as amphoteric and anionic surfactants suitable for use in the invention can be readily ascertained, in view of the

foregoing description, from McCutcheon's Detergents and Emulsifiers, North American Edition, McCutcheon Division, MC Publishing Co., Glen Rock, N.J. 07452 and the CTFA International Cosmetic Ingredient Handbook, Published by The Cosmetic, Toiletry, and Fragrance Association, Washington, D.C.

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

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

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

In addition to buffering agents, in some instances it may be desirable to include chelating or sequestering agents in the present compositions in order

to bind metal ions, which might otherwise react with the lens and/or protein deposits and collect on the lens. Ethylene-diaminetetraacetic acid ("EDTA") and its salts (disodium) are preferred examples. They are usually added in amounts ranging from about 0.01 to about 0.3 weight percent. Other suitable sequestering agents include phosphonic acids, gluconic acid, citric acid, tartaric acid, and their salts; e.g., sodium salts.

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

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

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

Methods of Administration

In embodiments wherein a PKC- δ inhibitor comprises a nucleic acid molecule, such molecule can be administered into a subject using *in vivo* gene therapy techniques (such as those disclosed in U.S. Pat. No. 5,399,346; which is incorporated herein by reference in its entirety). The nucleic-acid PKC- δ inhibitor incorporated into cells (e.g., ocular cells) of the host suppresses the *in vivo* activity of PKC- δ and produces neuroprotection to the subject.

For *in vivo* administration, the cells can be in the subject and the nucleic acid can be administered in a pharmaceutically acceptable carrier. The subject can be any animal in which it is desirable to selectively express a nucleic acid in a cell. In a preferred embodiment, the animal of the present invention is a human. In addition, non-human animals which can be treated by a method of this invention can include, but are not limited to, non-human primates, cats, dogs, birds, horses, cows, goats, sheep, guinea pigs, hamsters, gerbils and rabbits, as well as any other animal in which selective expression of a nucleic acid in a cell can be carried out according to the methods described herein.

In the method described above, which includes the introduction of an exogenous nucleic acid into the cells of a subject (i.e., gene transduction or transfection), a nucleic acid of the present invention can be in the form of naked DNA or RNA or the nucleic acids can be in a vector for delivering the nucleic acid

to the cells for expression of the nucleic acid inside the cell. The vector can be a commercially available preparation, such as those disclosed herein above. Delivery of the nucleic acid or vector to cells can be via a variety of mechanisms. As one example, delivery can be via a liposome, using commercially available liposome preparations such as Lipofectin[®], Lipofectamine[®] (GIBCO-BRL, Inc., Gaithersburg, Maryland), Superfect[®] (Qiagen Inc., Valencia, California) and Transfectam[®] (Promega Biotec, Inc., Madison, Wisconsin), as well as other liposomes developed according to procedures standard in the art. In addition, the nucleic acid or vector of this invention can be delivered in vivo by electroporation, the technology for which is available from Genetronics, Inc. (San Diego, California) as well as by means of a sonoporation machine (ImaRx Pharmaceutical Corp., Tucson, Arizona).

As one example, vector delivery can be via a viral system, such as a retroviral vector system which can package a recombinant retroviral genome. The recombinant retrovirus can then be used to infect and thereby deliver nucleic acid to the infected cells. The exact method of introducing the nucleic acid into mammalian cells is, of course, not limited to the use of retroviral vectors. Other techniques are widely available for this procedure including the use of adenoviral vectors, adeno-associated viral ("AAV") vectors, lentiviral vectors, pseudotyped retroviral vectors, and pox virus vectors, such as vaccinia virus vectors. Physical transduction techniques can also be used, such as liposome delivery and receptor-mediated and other endocytosis mechanism. A method disclosed herein can be used in conjunction with any of these or other commonly used gene transfer methods.

The nucleic acid and the nucleic acid delivery vehicles of this invention, (e.g., viruses; liposomes, plasmids, vectors) can be in a pharmaceutically acceptable carrier for in vivo administration to a subject. By "pharmaceutically acceptable" is meant a material that is not biologically or otherwise undesirable,

i.e., the material may be administered to a subject, along with the nucleic acid or vehicle, without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained. The carrier would naturally be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art.

The nucleic acid or vehicle may be administered orally, parenterally (e.g., intravenously), by intramuscular injection, by intraperitoneal injection, transdermally, extracorporeally, topically or the like. The exact amount of the nucleic acid or vector required will vary from subject to subject, depending on the species, age, weight and general condition of the subject, the severity or mechanism of any disorder being treated, the particular nucleic acid or vehicle used, its mode of administration and the like.

The compounds of this invention (e.g., nucleic acids, proteins, polypeptides, or small molecules) can be administered to a cell of a subject either *in vivo* or *ex vivo*. For administration to a cell of the subject *in vivo*, as well as for administration to the subject, the compounds of this invention can be administered orally, parenterally (e.g., intravenously), by intramuscular injection, by intraperitoneal injection, subcutaneous injection, transdermally, extracorporeally, topically, mucosally or the like.

Depending on the intended mode of administration, the compounds of the present invention can be in pharmaceutical compositions in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, pills, capsules, powders, liquids, suspensions, lotions, creams, gels, or the like. The compositions will include, as noted above, an effective amount of the selected compound, possibly in combination with a pharmaceutically acceptable carrier

and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents, etc., many of which are disclosed herein.

Parenteral administration of the compounds of the present invention, if used, is generally characterized by injection. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. As used herein, "parenteral administration" includes intradermal, subcutaneous, intramuscular, intraperitoneal, intravenous and intratracheal routes. Parenteral administration can involve use of a slow release or sustained release system such that a constant dosage is maintained. See, e.g., US Patent 3,610,795, which is incorporated by reference herein. These compounds can be present in a pharmaceutically acceptable carrier, which can also include a suitable adjuvant.

The exact amount of the compound required will vary from subject to subject, depending on the species, age, weight and general condition of the subject, the particular compound used, its mode of administration and the like. An appropriate amount can be determined by one of ordinary skill in the art using only routine experimentation given the teachings herein.

If *ex vivo* methods are employed, cells or tissues can be removed and maintained outside the subject's body according to standard protocols well known in the art. The compounds of this invention can be introduced into the cells via known mechanisms for uptake of small molecules into cells (e.g., phagocytosis, pulsing onto class I MHC-expressing cells, liposomes, etc.). The compounds of this invention can also be linked to the homeodomain of Antennapedia for introduction, i.e. internalization of the compound, into cells (P. Prochiantz, *Curr. Opin. Neurobiol.*, Vol. 6, No. 5, 629 (1996)). The cells can then be infused (e.g., in a pharmaceutically acceptable carrier) or transplanted back into

the subject per standard methods for the cell or tissue type. Standard methods are known for transplantation or infusion of various cells into a subject.

The following examples serve to illustrate some non-limiting compositions of the present invention. The ingredients shown in each of Tables 1-10 are mixed to form a pharmaceutical composition for treating or controlling ocular neurodegenerative conditions. The composition may be further sterilized prior to administration to the subject, according to known methods of sterilization of pharmaceutical compositions.

EXAMPLE 1:

Table 1

Ingredient	Amount (percent w/v)
Polyhexamethylenebiguanide HCl (as a 20 percent w/w solution available under the mark Cosmocil CQ, from ICI Chemical Co.)	0.00047
Boric acid	0.64
Sodium borate	0.12
Edetate disodium	0.11
Sodium chloride	0.49
Poloxamine (Tetronic® 1107 from BASF)	1.00
Tetrasodium etidronate (as a 30 percent w/w solution, available under the mark DeQuest® 2016 from Monsanto Co.)	0.01
Rottlerin	0.02
Hydrochloric acid (1N) or sodium hydroxide (1N)	as required to adjust pH to 7-7.5
Purified water	q.s. to 100

EXAMPLE 2:

Table 2

Ingredient	Amount (percent w/v)
Polyhexamethylenebiguanide HCl (as a 20 percent w/w solution available under the mark Cosmocil CQ, from ICI Chemical Co.)	0.00047
Boric acid	0.64
Sodium borate	0.12
Edetate disodium	0.11
Sodium chloride	0.49
Polysorbate 80	0.7
Short peptide having SEQ. NO. 9 (SFNSYELGSL)	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 3:

Table 3

Ingredient	Amount (percent w/v)
Polyhexamethylenebiguanide HCl (as a 20 percent w/w solution available under the mark Cosmocil CQ, from ICI Chemical Co.)	0.0006
Phosphate buffer	0.5
Edetate disodium	0.11
Sodium chloride	0.49
Polysorbate 80	0.7
Tetrasodium etidronate (as a 30 percent w/w solution, available under the mark DeQuest® 2016 from Monsanto Co.)	0.01
PKC- δ Antibody “ab4143” from Abcam Inc., Cambridge, Massachusetts, having SEQ. NO. 7	0.02
Purified water	q.s. to 100

EXAMPLE 4:

Table 4

Ingredient	Amount (percent w/v)
Polyhexamethylenebiguanide HCl (as a 20 percent w/w solution available under the mark Cosmocil CQ, from ICI Chemical Co.)	0.0005
Boric acid	0.64
Sodium borate	0.12
Edetate disodium	0.11
Sodium chloride	0.49
Polysorbate 80	0.7
PKC- δ Antibody “ab57419” from Abcam Inc., Cambridge, Massachusetts, having SEQ. NO. 8	0.03
Hydrochloric acid (1N) or sodium hydroxide (1N)	as required to adjust pH to 7-7.5
Purified water	q.s. to 100

EXAMPLE 5:

Table 5

Ingredient	Amount (percent w/v)
Polyhexamethylenebiguanide HCl (as a 20 percent w/w solution available under the mark Cosmocil CQ, from ICI Chemical Co.)	0.0005
Boric acid	0.64
Sodium borate	0.12
Edetate disodium	0.11
Sodium chloride	0.49
Polysorbate 80	0.7
Tetrasodium etidronate (as a 30 percent w/w solution, available under the mark DeQuest® 2016 from Monsanto Co.)	0.01
Anti-human PKC- δ monoclonal antibody GTX93022, humanized (GTX93022 is a product of Gextex, San Antonio, Texas)	0.02
Hydrochloric acid (1N) or sodium hydroxide (1N)	as required to adjust pH to 7-7.5
Purified water	q.s. to 100

EXAMPLE 6:

Table 6

Ingredient	Amount (percent w/v)
Polyhexamethylenebiguanide HCl (as a 20 percent w/w solution available under the mark Cosmocil CQ, from ICI Chemical Co.)	0.00047
Boric acid	0.64
Sodium borate	0.12
Edetate disodium	0.11
Sodium chloride	0.49
Polysorbate 80	0.7
Tetrasodium etidronate (as a 30 percent w/w solution, available under the mark DeQuest® 2016 from Monsanto Co.)	0.01
Chloroquine	0.001
siRNA having SEQ. NO. 3	0.01
Hydrochloric acid (1N) or sodium hydroxide (1N)	as required to adjust pH to 7-7.5
Purified water	q.s. to 100

EXAMPLE 7:

Table 7

Ingredient	Amount (percent w/v)
Polyhexamethylenebiguanide HCl (as a 20 percent w/w solution available under the mark Cosmocil CQ, from ICI Chemical Co.)	0.0005
Boric acid	0.64
Sodium borate	0.12
Edetate disodium	0.11
Sodium chloride	0.49
Polysorbate 80	0.7
Plasmid 10819 from Addgene, Cambridge, Massachusetts	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 (percent w/v)
Polyhexamethylenebiguanide HCl (as a 20 percent w/w solution available under the mark Cosmocil CQ, from ICI Chemical Co.)	0.0005
Boric acid	0.64
Sodium borate	0.12
Edetate disodium	0.11
Sodium chloride	0.49
Polysorbate 80	0.7
Tetrasodium etidronate (as a 30 percent w/w solution, available under the mark DeQuest® 2016 from Monsanto Co.)	0.01
Peptide SEQ. NO. 10	0.02
Hydrochloric acid (1N) or sodium hydroxide (1N)	as required to adjust pH to 7-7.5
Purified water	q.s. to 100

EXAMPLE 9:

Table 9

Ingredient	Amount (percent w/v)
Urea peroxide	0.06
Boric acid	0.64
Sodium borate	0.12
Edetate disodium	0.11
Sodium chloride	0.49
Polysorbate 80	0.7
Tetrasodium etidronate (as a 30 percent w/w solution, available under the mark DeQuest® 2016 from Monsanto Co.)	0.01
Peptide SEQ. NO. 11	0.02
Hydrochloric acid (1N) or sodium hydroxide (1N)	as required to adjust pH to 7-7.5
Purified water	q.s. to 100

EXAMPLE 10:

Table 10

Ingredient	Amount (percent w/v)
Polyquaternium-1	0.005
Boric acid	0.64
Sodium borate	0.12
Edetate disodium	0.11
Sodium chloride	0.49
Poloxamine (Tetronic® 1107 from BASF)	1.00
Peptide SEQ. NO. 13	0.05
Cyclosporine	0.05
Hydrochloric acid (1N) or sodium hydroxide (1N)	as required to adjust pH to 7-7.5
Purified water	q.s. to 100

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

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

The present invention also provides a method for treating or controlling degeneration of at least a component of the optic nerve system. The method comprises applying a composition to the eye, wherein the composition comprises compound that substantially inhibits, reduces, or interferes with, an

activity of a cell signaling cascade involving PKC- δ , antagonizes PKC- δ , or inhibits the activation of PKC- δ , or a combination thereof, in an effective amount for treating or controlling such degeneration.

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

In one embodiment, a composition of the present invention can be injected intravitreally to control the progression of an ocular neurodegenerative disease, using a fine-gauge needle, such as 25-33 gauge. Typically, an amount from about 25 μ l to about 100 μ l of a composition comprising one or more PKC- δ inhibitors is administered into a patient. A concentration of such a PKC- δ inhibitor or combination thereof is selected from the ranges disclosed above.

In another aspect, one or more PKC- δ inhibitors is incorporated into an ophthalmic device or system that comprises a biodegradable material, and the device is implanted into the posterior cavity of a diseased eye to provide a long-term (e.g., longer than about 1 week, or longer than about 1, 2, 3, 4, 5, or 6 months) control of progression of an ocular neurodegenerative disease. In one aspect, such control is achieved by reducing the levels of pro-inflammatory cytokines in tissues of the retina or optic nerve system over a long period of time.

In still another aspect, a method for controlling progression of an ocular degenerative disease comprises: (a) providing a composition comprising one or more PKC- δ inhibitors; and (b) administering to a subject an effective amount of the composition at a frequency sufficient to control the progression of the ocular degenerative disease.

In one embodiment, one or more PKC- δ inhibitors are selected from among those disclosed above.

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

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

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

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

COMBINATION THERAPY

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

High doses may be required for some currently used therapeutic agents, or high frequency for currently used methods, to achieve levels to effectuate the target response, but may often be associated with a greater frequency of adverse effects. Thus, combined use of a composition of the present invention, with agents or methods commonly used to control progression of ocular nerve damage allows the use of relatively lower doses of such other agents, or frequency of such other methods, resulting in a lower

frequency of potential adverse side effects associated with long-term administration of such therapeutic agents or methods. Thus, another indication of the compositions in this invention is to reduce adverse side effects of prior-art drugs or methods used to control optic nerve degeneration, such as the development of cataracts with long-acting anticholinesterase agents including demecarium, echothiophate, and isofluorophate.

In still another aspect, the present invention provides a method for preparing a composition for the treatment or control of an ocular neurodegenerative condition in a subject, which has an etiology in inflammation. The method comprises combining at least a PKC- δ inhibitor with a pharmaceutically acceptable carrier. The method may further including adding one or more pharmaceutically acceptable additives for providing certain desirable properties to the composition.

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

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

Glucocorticoids (“GCs”) are among the most potent drugs used for the treatment of allergic and chronic inflammatory diseases. However, as mentioned above, long-term treatment with GCs is often associated with numerous adverse side effects, such as diabetes, osteoporosis, hypertension, glaucoma, or cataract. These side effects, like other physiological manifestations, are results of aberrant expression of genes responsible for such diseases.

Research in the last decade has provided important insights into the molecular basis of GC-mediated actions on the expression of GC-responsive genes. GCs exert most of their genomic effects by binding to the cytoplasmic GC receptor ("GR"). The binding of GC to GR induces the translocation of the GC-GR complex to the cell nucleus where it modulates gene transcription either by a positive (transactivation) or negative (transrepression) mode of regulation. There has been growing evidence that both beneficial and undesirable effects of GC treatment are the results of undifferentiated levels of expression of these two mechanisms; in other words, they proceed at similar levels of effectiveness. Although it has not yet been possible to ascertain the most critical aspects of action of GCs in chronic inflammatory diseases, there has been evidence that it is likely that the inhibitory effects of GCs on cytokine synthesis are of particular importance. GCs inhibit the transcription, through the transrepression mechanism, of several cytokines that are relevant in inflammatory diseases, including IL-1 β (interleukin-1 β), IL-2, IL-3, IL-6, IL-11, TNF- α (tumor necrosis factor- α), GM-CSF (granulocyte-macrophage colony-stimulating factor), and chemokines that attract inflammatory cells to the site of inflammation, including IL-8, RANTES, MCP-1 (monocyte chemotactic protein-1), MCP-3, MCP-4, MIP-1 α (macrophage-inflammatory protein-1 α), and eotaxin. P.J. Barnes, *Clin. Sci.*, Vol., Vol. 94, 557-572 (1998). On the other hand, there is persuasive evidence that the synthesis of I κ B kinases, which are proteins having inhibitory effects on the NF- κ B pro-inflammatory transcription factors, is increased by GCs. These pro-inflammatory transcription factors regulate the expression of genes that code for many inflammatory proteins, such as cytokines, inflammatory enzymes, adhesion molecules, and inflammatory receptors. S. Wissink et al., *Mol. Endocrinol.*, Vol. 12, No. 3, 354-363 (1998); P.J. Barnes and M. Karin, *New Engl. J. Med.*, Vol. 336, 1066-1077 (1997). Thus, both the transrepression and transactivation functions of GCs directed to different genes produce the beneficial effect of inflammatory inhibition. On the other hand, steroid-induced diabetes and glaucoma appear to

be produced by the transactivation action of GCs on genes responsible for these diseases. H. Schäcke et al., *Pharmacol. Ther.*, Vol. 96, 23-43 (2002). Thus, while the transactivation of certain genes by GCs produces beneficial effects, the transactivation of other genes by the same GCs can produce undesired side effects. Therefore, in another aspect, the present invention provides pharmaceutical compositions for the treatment, reduction, alleviation, or amelioration of a pathological condition having an etiology in inflammation, which compositions avoid generation of one or more adverse side effects of GCs.

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

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

In still another aspect, said at least a prior-art glucocorticoid is selected from the group consisting of 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide,

chloroprednisone, clobetasol, clobetasone, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difluprednate, enoxolone, fluazacort, fluccloronide, 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

PKC- δ inhibitors 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 PKC- δ 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 PKC- δ inhibitor or a glucocorticoid), and then the TAT activity is measured. The TAT activities for the selected PKC- δ 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 PKC- δ inhibitor for the same condition.

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

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

SEQUENCE LISTING

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Lys Ala Arg Leu Ser Tyr Ser Asp Lys Asn Leu Ile Asp Ser Met Asp
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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 at least a PKC- δ inhibitor; wherein said at least a PKC- δ inhibitor is present at a concentration such that the composition is capable of treating or controlling degeneration of at least a component of an optic nerve system in a subject.
2. The composition of claim 1, further comprising an anti-inflammatory medicament.
3. The composition of claim 1, wherein said degeneration is a result of a disease selected from the group consisting of glaucoma, AMD, DR, retinitis pigmentosa, and combinations thereof.
4. The composition of claim 1, wherein said at least a PKC- δ inhibitor comprises rottlerin.
5. The composition of claim 1, wherein said at least a PKC- δ inhibitor is selected from the group consisting of antibodies to PKC- δ .
6. The composition of claim 5, wherein said PKC- δ is human PKC- δ .
7. The composition of claim 1, wherein said at least a PKC- δ inhibitor comprises a short peptide PKC- δ antagonist.
8. The composition of claim 1, wherein said at least a PKC- δ inhibitor comprises a PKC- δ antisense nucleic acid sequence.
9. The composition of claim 1, wherein said at least a PKC- δ inhibitor comprises a PKC- δ siNA, siRNA, dsRNA, miRNA, shRNA, or combination thereof.

10. The composition of claim 1, wherein said at least a PKC- δ inhibitor is present in an amount in a range from about 0.0001 to about 10 percent by weight of said composition.
11. The composition of claim 2, wherein said anti-inflammatory medicament comprises a material selected from the group consisting of non-steroidal anti-inflammatory drugs, peroxisome proliferator-activated receptor ("PPAR") ligands, and combinations thereof.
12. The composition of claim 11, wherein said anti-inflammatory medicament is selected from the group consisting of PPAR α ligands, PPAR δ ligands, PPAR γ ligands, and combinations thereof.
13. The composition of claim 1, further comprising a medicament selected from the group consisting of immunosuppressants, cyclooxygenase-2 inhibitors, DMARDS (disease-modifying anti-rheumatic drugs), anti-cell adhesion molecules, and combinations thereof.
14. The composition of claim 13, wherein said immunosuppressants are selected from the group consisting of cyclosporine, tacrolimus, rapamycinazathioprine, 6-mercaptopurine, and combinations thereof.
15. The composition of claim 1, wherein the composition has a pH in a range from about 5 to about 8.
16. A composition comprising: (a) at least a PKC- δ inhibitor; and (b) an additional medicament selected from the group consisting of NSAIDs, PPAR ligands, immunosuppressants, cyclooxygenase-2 inhibitors, DMARDS, anti-cell adhesion molecules, and combinations thereof; wherein the composition is capable of treating or controlling degeneration of a component of an optic nerve system; wherein each of said at least a PKC- δ inhibitor and said additional

medicament, when present, is present in an amount from about 0.0001 to about 5 percent by weight of said composition; and said composition has a pH of about 5-8.

17. A method for treating or controlling degeneration of a component of an optic nerve system in a subject, the method comprising administering to an environment of an affected eye a pharmaceutically effective amount of a composition that comprises at least a PKC- δ inhibitor, wherein said composition is administered at a frequency effective to provide said treating or controlling.
18. The method of claim 17, wherein said degeneration is a result of a disease selected from the group consisting of glaucoma, AMD, DR, retinitis pigmentosa, and combinations thereof.
19. The method of claim 18, wherein said at least a PKC- δ inhibitor comprises an antibody to PKC- δ .
20. The method of claim 19, wherein said PKC- δ is human PKC- δ .
21. The method of claim 18, wherein said at least a PKC- δ inhibitor comprises a short peptide antagonist to human PKC- δ .
22. The method of claim 18, wherein said at least a PKC- δ inhibitor comprises a PKC- δ antisense nucleic acid molecule.
23. The method of claim 18, wherein said at least a PKC- δ inhibitor comprises a PKC- δ siNA, siRNA, dsRNA, miRNA, shRNA, or combination thereof.
24. The method of claim 18, wherein said at least a PKC- δ inhibitor is present in an amount in a range from about 0.0001 to about 10 percent by weight of said composition.

25. The method of claim 17, wherein the composition further comprises an additional medicament selected from the group consisting of NSAIDs, PPAR ligands, immunosuppressants, cyclooxygenase-2 inhibitors, DMARDS, anti-cell adhesion molecules, and combinations thereof; wherein said additional medicament is present in an amount from about 0.0001 to about 5 weight percent.
26. The method of claim 24, wherein the composition further comprises an additional medicament selected from the group consisting of NSAIDs, PPAR ligands, immunosuppressants, cyclooxygenase-2 inhibitors, DMARDS, anti-cell adhesion molecules, and combinations thereof; wherein said additional medicament is present in an amount from about 0.0001 to about 5 weight percent.
27. A method for preparing a composition for treating or controlling degeneration of a component of an optic nerve system, the method comprising combining at least a PKC- δ inhibitor with a pharmaceutically acceptable carrier; wherein said at least a PKC- δ inhibitor is present at a concentration such that the composition is capable of treating or controlling said degeneration in a subject.
28. The method of claim 27, further comprising adding a medicament selected from the group consisting of NSAIDs, PPAR ligands, immunosuppressants, cyclooxygenase-2 inhibitors, DMARDS, anti-cell adhesion molecules, and combinations thereof to the composition.