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 (54) Title: METHODS AND COMPOSITIONS FOR TREATING AND PREVENTING POSTERIOR SEGMENT OPHTHALMIC DISORDERS

(57) **Abrégé/Abstract:**

Methods and compositions for the prophylactic and therapeutic treatment of ophthalmic disorders associated with the posterior segment of the eye using topical ophthalmic compositions comprising therapeutic agents. The invention specifically provides for methods and compositions for the prophylactic and therapeutic treatment of retinal disorders associated with neovascularization using topical ophthalmic compositions comprising hydroxamic acid matrix metalloproteinase inhibitors such as batimastat.

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(54) Title: METHODS AND COMPOSITIONS FOR TREATING AND PREVENTING POSTERIOR SEGMENT OPHTHALMIC DISORDERS

(57) Abstract: Methods and compositions for the prophylactic and therapeutic treatment of ophthalmic disorders associated with the posterior segment of the eye using topical ophthalmic compositions comprising therapeutic agents. The invention specifically provides for methods and compositions for the prophylactic and therapeutic treatment of retinal disorders associated with neovascularization using topical ophthalmic compositions comprising hydroxamic acid matrix metalloproteinase inhibitors such as batimastat.

METHODS AND COMPOSITIONS FOR TREATING AND PREVENTING POSTERIOR SEGMENT OPHTHALMIC DISORDERS

FIELD OF THE INVENTION

This invention relates to ophthalmic disorders, and more particularly to the prophylactic and therapeutic treatment of disorders associated with the posterior segment of the eye using topical ophthalmic compositions.

BACKGROUND OF THE INVENTION

Posterior segment ophthalmic disorders affect the posterior segment of the eye, *i.e.*, the vitreous body, retina, optic nerve, and choroid. These disorders include such conditions as pathological neovascularization and ectopic proliferation, atrophy and nerve cell death, inflammation and infection, and detachment. Diseases and conditions commonly associated with these symptoms include macular degeneration, diabetic retinopathy, retinopathy of prematurity, retinitis pigmentosa, macular edema, glaucoma, posterior uveitis, endophthalmitis, ocular insult and ocular manifestation of systemic disease such as viral infection, arthritis and rosacea.

Atrophic and proliferative diseases of the vasculature and cells that support the posterior segment are primary causes of blindness in the world. Two vascular systems, retinal and uveal, support the posterior segment. The retinal vasculature is a complex of arteries and veins that supports the metabolic need of the neurons in the inner retina. With the exclusion of the fovea, which is a specialized region of photoreceptor cells in the center of the macula that is responsible for sharp color vision, the retina is comprised of 8 different cell types organized in 10 parallel layers. Light from the outside passes through the cornea, lens and vitreous and is focused on the macula, the region of highest visual acuity in the retina. Photoreceptors in the outer retina transduce light into neurochemical signals that are processed by retinal neurons and transmitted to the brain by the optic nerve. The uvea is a system of capillaries and arteries that lies just below the connective tissue exterior of the eye. The posterior part of the uvea, the choroid, is a layer of pigmented blood vessels sandwiched between the sclera and the retina. With the exception of the liver, the choroid

has the richest blood supply of any vascular plexus, primarily to handle the metabolic needs of photoreceptors and the retinal pigment epithelium (RPE) . The forward part of the uvea, the ciliary body, and the iris are more complex. However, infection in these anterior segment tissues is easily spread to the posterior segment by way of the uveal tract.

Neovascularization is a proliferative disease of endothelial cells which form the structural elements of blood vessels. Blood vessels grow and proliferate in a tissue, typically in response to a decrease in blood flow to the tissue. Neovascularization typically improves the flow of blood in a tissue by creating new blood vessels instead of replacing the existing vasculature. Pathological neovascularization involves both the degradation of tissue through enzymatic action and the formation of new immature blood vessels and fibrous membranes in ectopic locations. The formation of new blood vessels may compromise the function and complex architecture of arteries and veins in the uvea, retina, and choroid and ultimately cause the permanent loss of vision as a result of hemorrhaging and scarring. Trophic factors secreted by neovascular elements and adhesions produced from fibrous neovascular membranes further degrade visual function through detachment of the retina and the invasion of normally avascular regions with cytokines and inflammatory elements.

Neovascular diseases of the posterior segment of the eye include diabetic retinopathy, age-related macular degeneration (also known as wet or exudative macular degeneration), neovascular glaucoma, retinopathy of prematurity, sickle-cell retinopathy, retinal vein occlusion, oxygen induced retinopathy, and neovascularization due to ocular insults such as traumatic or surgical injury or transplantation of eye tissue. Other conditions or diseases associated with the manifestation of retinal neovascularization include any disease or condition where a part of the retina is subject to a relatively non-perfused state compared to surrounding tissue, where any one or more of the proteins, proteinases, hormones, or cellular signals associated with neovascularization are detected, or where new vessel growth can be detected or observed. In addition, diseases implicating matrix metalloproteinase (MMP) activity, endothelial cell invasion, or the generation of new blood

vessels may also be associated with pathological neovascularization according to this invention.

Intraocular spaces in which inflammatory and immune responses can occur are the vitreous cavity and subretinal space. Constitutive expression of membrane-bound and soluble immunomodulatory factors and the induction of systemic immune deviation give the healthy eye a unique immunoprivileged microenvironment. However, when posterior segment ocular inflammation does occur, it is an important cause of blindness. According to this invention inflammatory diseases are those that display one of four distinct clinical features: variably sized chorio-retinal infiltrates of inflammatory cells; retinal vessel inflammation; vitreous cellular infiltrates; and edema of the macula, optic nerve head or entire retina. Other conditions include those where cells or cytokine profiles consistent with infection and inflammation can be detected. Inflammation is a special class of proliferative disease in which the proliferative elements are cells of the immune system. In these cases the tissue reacts to chemicals secreted by immune cells that are normally dormant or have been recruited to the site of inflammation. Inflammatory responses in the posterior segment may result from hypersensitivity (allergy), infectious agents, or unknown immunopathic cause. In hypersensitive inflammation, eosinophils are recruited. Upon degranulation these cells stimulate the release of a variety of mediators including granule proteins, prostaglandins, and cytokines that perpetuate the inflammatory response. When an infectious agent is the cause, the appropriate treatment is often straightforward, but appropriate drugs may have high side effect profiles.

Atrophic disorders of the posterior segment are diseases in which differentiated cells die and compromise vision. Cell death may be triggered by both environmental and genetic factors and may be distinguished as either apoptosis or necrosis. Atrophic cell death is not equivalent to normal programmed cell death that occurs during the developmental phase of the eye and its vasculature. For the purposes of this invention, atrophic diseases of the posterior segment include retinal atrophy that is triggered by trauma, systemic disease, vascular insufficiency, cellular senescence, or cytotoxic insult.

Age-related macular degeneration (ARMD) is one of the leading causes of blindness in older adults in the United States. The atrophic form of the disease (described below) accounts for 85% of the cases. The "wet" or exudative form is a neovascular disease that causes 90% of the blindness in Americans of European descent over the age of 65. Wet ARMD is characterized by loss of central vision, usually in both eyes, due to damage to the retinal pigment epithelial (RPE) cells and invasion of the avascular outer retina by immature blood vessels from the choroid capillaries. The invasion involves a breach of the RPE cell layer which constitutes the blood-retinal barrier. When invasion involves the macula, patients have serious visual impairment. The natural course of neovascularization in ARMD is the development of a disciform scar over the macula and irreversible blindness. In addition to their role in the regeneration of visual chromophore, 11-cis retinal, RPE cells partition the photoreceptor cells from the vascular layers of the choroid. The tissue invasion and degradation characteristic of neovascularization, and the loss of RPE and photoreceptor cells is facilitated by the action of proteinases, MMPs and the altered expression of integrins and integrin-binding elements. Alterations in the metabolism of invading blood vessels and invaded tissue (Bruch's membrane, RPE, and retina) also occur, and may result from a variety of events, such as the dysregulation of growth factors, the up-regulation of vascular endothelial growth factor (VEGF) and other molecules that signal proliferation, and the down-regulation of basic fibroblast growth factor (bFGF) and other signal molecules that regulate MMP activity. See Plantner JJ *et al.*, *Exp Eye Res.* 67(6):637-45 (1998); Guo L *et al.*, *Invest Ophthalmol Vis Sci.* 40(11):2676-82 (1999); Steen B *et al.*, *Invest Ophthalmol Vis Sci.* 39(11):2194-200 (1998).

Diabetic retinopathy is the leading cause of blindness among working age adults in the United States. It is observed in up to ninety percent of patients with insulin dependent diabetes mellitus of long-term duration (more than 10 years). Klein *et al.*, *Arch. Opth.* 112:1217 (1994). Initially, the high blood glucose levels common to persons with diabetes mellitus cause an increase in glycosated proteins and growth factor levels in the eyes. This condition known as the "pre-diabetic retinopathy stage" and can lead to retinopathy if not prophylactically treated. Non-proliferative or early-stage diabetic retinopathy, also known

as "background diabetic retinopathy," is characterized by thickening of the basement membrane, loss of retinal pericytes, microvascular abnormalities, intraretinal microaneurysms, retinal hemorrhages (known as "dot blot" or "cotton wool" spots), retinal edema, capillary closure, and soft and hard exudates. Late-stage or proliferative diabetic retinopathy is characterized by neovascularization and fibrovascular growth, *i.e.*, scarring involving glial and fibrous elements, from the retina or optic nerve over the inner surface of the retina or into the vitreous cavity. At active neovascularization sites, both the high (54 kD) and low (33 kD) molecular weight forms of the protein urokinase have been found at levels significantly higher than in normal retinas. The levels of both pro and active forms of the matrix metalloproteinases MMP-2 (gelatinase A) and MMP-9 (gelatinase B) are also significantly elevated in neovascular membranes in comparison to normal membranes. *See Das et al.*, *Investigative Ophthalmology & Visual Sciences* 40:809-13 (1999); *Coors et al.*, *Investigative Ophthalmology & Visual Sciences* 40(4):S231 (1999). Typically the active forms of MMPs such as collagenase, stromelysin and gelatinase are not present at detectable levels in normal retinas.

Retinopathy of prematurity (ROP) is a common cause of blindness in children in the United States and the developed world. Premature infants are exposed to hyperoxic conditions after birth due to the higher partial pressure of oxygen in the atmosphere as compared to *in utero* conditions. Supplemental oxygen is necessary for the survival of premature infants, yet may result in ROP. The hyperoxic atmosphere causes retinal blood vessels to stop developing into the peripheral retina, resulting in ischemia and localized hypoxic conditions as the metabolic demands of the developing retina increase. The resulting localized hypoxia stimulates retinal neovascularization and fibrovascular growth into and above the retina and the vitreous. The neovascularization usually regresses, but may lead to irreversible vision loss. The therapeutic approach to ROP is prevention. *See Gaynon MW and Stevenson DK, Pediatrics* 105(2):295-310 (2000); *Phelps DL et al., Cochrane Database Syst Rev.* (2):CD001073 (2000). However, in severe cases laser diode, vitrectomy, or retinal ablation surgery may be unavoidable. There are at least 10,000 new cases per year of ROP with a worldwide estimate of 10 million total cases.

Glaucoma is a group of diseases characterized by a particular pattern of blindness involving damage to the optic nerve and visual field loss. Increased intra-ocular pressure is a risk factor and contributes to some but not all cases of optic nerve atrophy and retinal cell death in the glaucomatous eye. Race is a predisposing factor for severe glaucoma. People of African descent are six times more likely than those of European descent to develop bilateral blindness. Even when elevated intraocular pressure (IOP) is not exhibited, glaucomatous cell death occurs in the retina. Optic nerve damage occurs when the separations between axon bundles in the optic nerve and the retinal nerve fiber layer degenerates. Treatment for glaucoma usually focuses on lowering the IOP, which may alleviate the symptoms but cannot prevent all cell death. *See Hitchings RA., Br J Ophthalmol.* 84(7):678-9 (2000); Ritch R., *Curr Opin Ophthalmol.* 11(2):78-84 (2000).

Atrophic cell death also occurs in “dry” or non-exudative age-related macular degeneration. Dry macular degeneration is the prevalent form of ARMD in patients over the age of 65. Unlike the neovascular form of the disease, race does not seem to be a risk factor in the development of dry ARMD. Early signs of the disease include a build up of material called drusen between the RPE and Bruch’s membrane which impairs diffusion of oxygen from the choroidal circulation. Advanced disease is characterized by RPE and photoreceptor cell death often in localized regions of the peripheral retina (geographic atrophy), as well as alterations in the Bruch’s membrane that prevents the proliferation and reattachment of RPE cells. Treatment for dry macular degeneration typically involves dietary supplementation with vitamin E and food supplements to enhance the metabolic capacity of the tissue and to restore the photoprotective pigments to the choroid and RPE. *See Delcourt C et al., Arch Ophthalmol.* 117(10):1384-90 (1999); Jacques PF, *Int J Vitam Nutr Res.* 69(3):198-205 (1999). Experimental surgical intervention to destroy drusen or transplant iris pigment epithelium or RPE cells may also be attempted. *See Friberg TR, Semin Ophthalmol.* 14(1):45-50 (1999); Abe T. *et al., Tohoku J Exp Med.* 189(4):295-305 (1999); Alverre PV *et al., Eur J Ophthalmol.* 9(3):217-30 (1999).

Retinitis pigmentosa (RP) is a group of inherited retinal diseases caused by mutations in photoreceptor or RPE proteins that affects 1 in 3000 individuals worldwide.

The most common forms of RP involve mutations that alter the function or production of rhodopsin. RP is characterized by the selective loss of rod photoreceptors, and night blindness. Advanced disease includes constriction of the visual field (tunnel vision) and peripheral blindness. Patients exhibiting RP are generally blind by their third decade.

Treatment for RP currently involves dietary supplementation with vitamin A palmitate. *See Fex GA et al., Graefes Arch Clin Exp Ophthalmol. Aug;234 Suppl 1:S18-21 (1996).*

Chronic macular edema is a frequently observed complication in RP patients. Treatment with oral carbonic anhydrase inhibitors (*e.g.*, acetazolamide) is commonly prescribed. *See Wolfensberger, TJ Doc Ophthalmol. 97(3-4):387-97 (1999).* Experimental gene therapy to replace photoreceptor proteins or enhance specific growth and survival factors has been successful in treating animal models of RP. *See Ali RR et al., Nat Genet. Jul;25(3):306-10 (2000); Lewin AS et al., Nat Med. Aug;4(8):967-71 (1998).*

Posterior uveitis is a group of sight-threatening inflammatory diseases of the back of the eye, including retinitis, retinochoroiditis, and choroiditis. Treatment for this condition generally involves systemic use of corticosteroid or other immuno-suppressive agents. However, systemic administration is not the ideal route of administration because of the potentially severe side effects.

Endophthalmitis is an inflammatory response to invading bacteria, or fungal and parasitic microorganisms. It generally involves the vitreous and retina and can lead to loss of sight within a short period of time, depending on the virulence of invading organisms and the degree of toxins produced by these organisms. It is a serious complication of cataract surgery, filtering procedures, and penetrating ocular injuries. The poor prognosis of the disease can be attributed mainly to the poor penetration of antibiotics into the back of the eye.

Known surgical and pharmacological treatments for posterior segment ophthalmic disease include surgical intervention such as vitrectomy, laser and radiotherapy, cryotherapy and pharmacological intervention such as chemotherapy. Panretinal laser coagulation is the classic treatment for proliferative diabetic retinopathy, but may have serious side effects such as foveal burns, hemorrhaging, retinal detachment, choroidal vessel growth, decreased

peripheral and night vision, and changes in color perception. Vitrectomy, cryotherapy and laser therapy may be used to treat ROP and other neovascular diseases, but are not completely effective and may damage the eye and result in decreased vision. In some diseases such as exudative cases of age-related macular degeneration, temporary prevention of vision loss may be achieved by laser or photodynamic therapy, but no permanent treatment is available for some forms of diseases associated with retinal neovascularization.

Drug therapy has advantages compared to micro and laser surgery in that the tissue invasion is smaller and the stress¹ placed on the ocular tissue is lower. The number of effective drugs, however, is quite small. In addition, patient compliance may be negatively influenced by systemic side effects. Compounds which inhibit the action of MMPs involved in connective tissue breakdown are of potential value in the treatment of angiogenesis-dependent diseases such as proliferative retinopathies, neovascular glaucoma, and other forms of retinal neovascularization. Certain agents have been proposed for inhibiting MMPs (*see* U.S. Patent No. 5,917,090). In particular, MMP inhibitors have been employed as potential treatments to the retina via intraorbital administration, tissue specific microinjection, or intravitreal injection (*see, e.g.*, European Patent Publication EP 0930067, published July 21, 1999; U.S. Patent No. 5,260,059; and published PCT Application WO 97/18835). While these treatments may act directly at the posterior segment, they have the disadvantage of being difficult to administer and of requiring the co-administration of anesthetic to the patient.

Topical treatment would be preferred because a topical composition may be self-administered by a patient, and does not require the co-administration of anesthetics. Topical compositions are generally ineffective at delivering a therapeutically effective amount of an active ingredient to the posterior segment, however, due to a lack of permeation through the conjunctiva, cornea, and sclera, and the presence of the blood-retinal barrier. Some ophthalmic treatment agents, such as the highly soluble β -blocking agents, have been found to reach the retina after topical administration because they are absorbed into the blood stream via the nasal mucosa or lid margin vessels and passed systemically to the retina (*see* Osborne et al., *Exp. Eye Res.* 69:331-42 (1999)). This method is ineffective for relatively

insoluble agents that do not pass through the blood-retinal barrier and is undesirable if treatment of one eye is required. In addition, absorption into the blood stream may result in systemic side effects that may not result from low concentration topical administration and direct absorption by ocular tissues.

What is needed is a topical ophthalmic composition for the prophylactic and therapeutic treatment of posterior segment ophthalmic disorders that is capable of delivering a therapeutically effective amount of an active ingredient to the posterior segment. Also needed are methods for prophylactic and therapeutic treatments of posterior segment ophthalmic disorders.

SUMMARY OF THE INVENTION

The present invention relates to the unexpected discovery that topical administration of the compositions of the present invention, which comprise a therapeutic agent, are capable of delivering a therapeutically effective amount of a therapeutic agent to the posterior segment. This discovery was unexpected because prior methods of topical administration of relatively insoluble compounds failed to result in therapeutically effective amounts of the compound reaching the posterior segment tissue and being retained therein.

The present invention provides methods for treating ophthalmic disorders in a mammal in need of such treatment, or preventing ophthalmic disorders in a mammal susceptible to developing such disorders, comprising topically administering to the eye a composition capable of delivering a therapeutically effective amount of a therapeutic agent to the posterior segment of the eye.

Other methods of the present invention include methods for treating posterior segment ophthalmic disorders in a mammal in need of such treatment, or preventing posterior segment ophthalmic disorders in a mammal susceptible to developing such disorders, comprising topically administering to the eye a composition capable of delivering a therapeutically effective amount of a therapeutic agent to the posterior segment of the eye, where the composition comprises a polymeric suspension agent and a therapeutic agent.

Further provided are methods for treating ophthalmic disorders in a mammal in need of such treatment, or preventing ophthalmic disorders in a mammal susceptible to developing such disorders, comprising administering topically to the eye a composition comprising a therapeutic agent and a polymeric suspension agent, where the composition is capable of delivering to the posterior segment of the eye a therapeutically effective amount of the therapeutic agent.

The present invention also provides ophthalmic compositions for use in treating or preventing posterior segment ophthalmic disorders in a mammal by topical administration to the eye comprising a therapeutically effective amount of a therapeutic agent, and ophthalmic compositions for use in treating or preventing posterior segment ophthalmic disorders in a mammal by topical administration to the eye comprising a therapeutically effective amount of a therapeutic agent and a polymeric suspension agent.

Further provided are topical ophthalmic compositions for use in treating or preventing posterior segment ophthalmic disorders in a mammal, comprising a therapeutic agent, where the compositions are capable of delivering a therapeutically effective amount of the therapeutic agent to the posterior segment of the eye. Topical ophthalmic compositions for use in treating or preventing posterior segment ophthalmic disorders in a mammal, comprising a therapeutic agent and a polymeric suspension agent, where the compositions are capable of delivering a therapeutically effective amount of the therapeutic agent to the posterior segment of the eye are also provided.

Also provided are topical ophthalmic compositions for use in treating or preventing retinal neovascularization in a mammal, comprising a batimastat compound and a polymeric suspension agent, where the composition is capable of delivering a therapeutically effective amount of the batimastat compound to the retina. Also provided are topical ophthalmic compositions for use in treating or preventing retinal neovascularization in a mammal, comprising about 0.1 to about 0.3 percent by weight of batimastat and about 0.5 to about 1.25 percent by weight of a polymeric suspension agent, where the composition is capable of delivering a therapeutically effective amount of batimastat to the retina, and topical ophthalmic compositions for use in treating or preventing retinal neovascularization in a

human, comprising about 0.1 to about 0.3 percent by weight of batimastat and about 0.5 to about 1.5 percent by weight of a polycarbophil, where the composition is capable of delivering a therapeutically effective amount of batimastat to the retina. Also provided for are ophthalmic compositions comprising the batimastat compounds at a concentration from about 0.01 to about 3 percent by weight; ophthalmic compositions comprising about 0.1 to about 0.3 percent by weight of the batimastat compounds and ophthalmic compositions comprising about 0.05 to about 0.5 percent by weight of batimastat compounds.

The polymeric suspension agents used in the methods and compositions of the present invention may comprise one or more polymers. In particular, cross-linked polymers, acrylic acid-containing polymers and carboxyl-vinyl-containing polymers may be used. Particularly preferred polymers include polycarbophil, the DuraSite® polymeric delivery system (InSite Vision, Inc., Alameda, CA), and mucomimetic polymers (*see, e.g.*, U.S. Patent No. 5,932,572).

Additional advantages and features of the present invention will be apparent from the following detailed description, drawings and examples which illustrate preferred embodiments of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts the effects of a therapeutic agent on the number of neovascularization events in a section of murine retinal tissue;

Figure 2 depicts the relative levels of MMP-9 activity in control, hyperoxic untreated, and hyperoxic treated murine retinal tissue;

Figure 3 depicts the relative levels of MMP-2 activity in control, hyperoxic untreated, and hyperoxic treated murine retinal tissue;

Figure 4 depicts the relative levels of urokinase activity in control, hyperoxic untreated, and hyperoxic treated murine retinal tissue; and

Figure 5 depicts the retinal tissue levels of batimastat over time following topical application to rabbit eyes.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Reference will now be made in detail to the presently preferred embodiments of the invention, which, together with the drawings and the following examples, serve to explain the principles of the invention. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention, and it is to be understood that other embodiments may be utilized, and that structural, biological, and chemical changes may be made without departing from the spirit and scope of the present invention.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are now described.

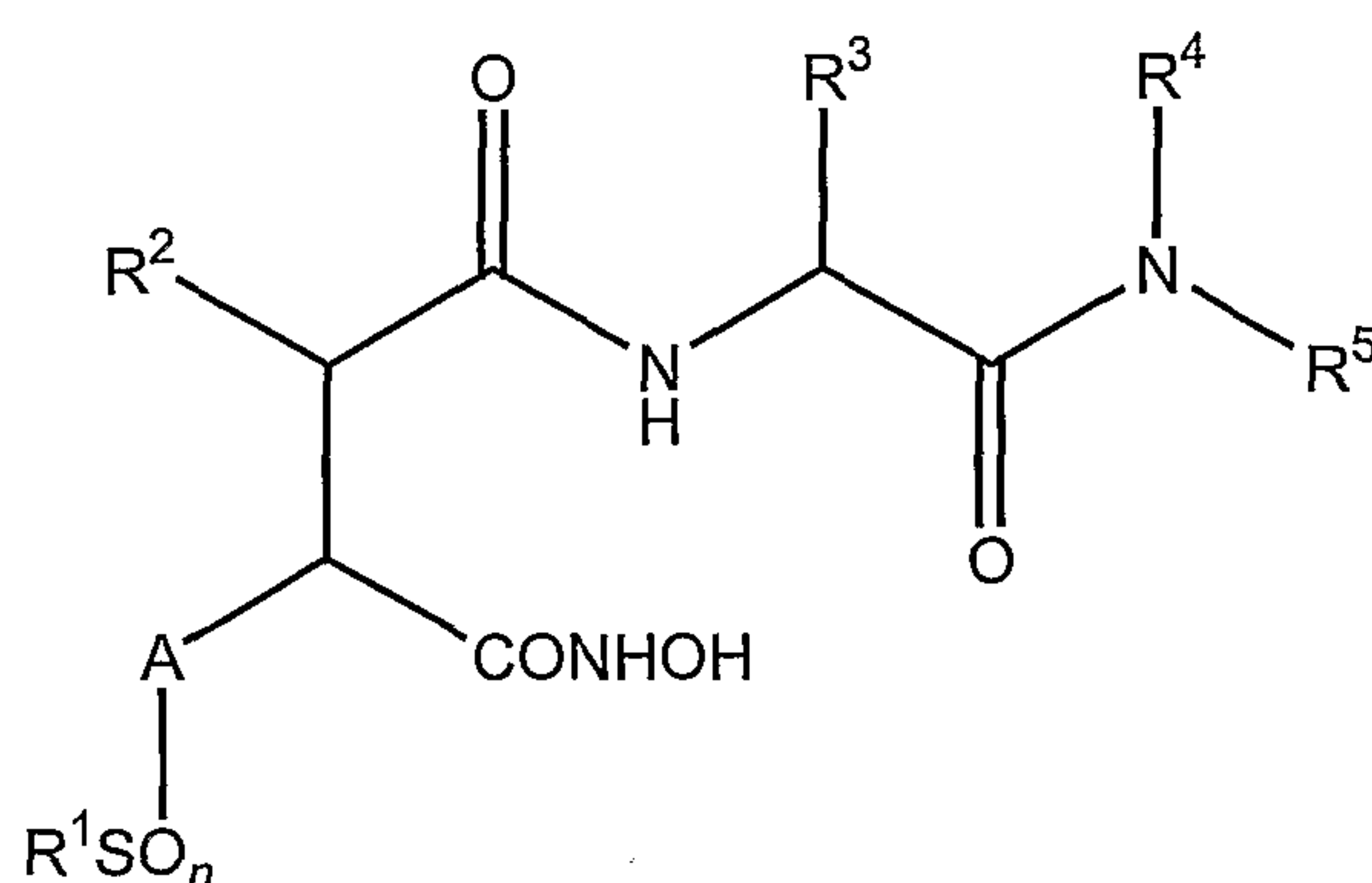
One skilled in the art may refer to general reference texts for detailed descriptions of known techniques discussed herein or equivalent techniques. These texts include Current Protocols in Molecular Biology (Ausubel *et al.*, eds., John Wiley & Sons, N.Y., and supplements through June 1999), Current Protocols in Immunology (Coligan *et al.*, eds., John Wiley & Sons, N.Y., and supplements through June 1999), Current Protocols in Pharmacology (Enna *et al.*, eds., John Wiley & Sons, N.Y., and supplements through June 1999), The Pharmacological Basis of Therapeutics (Fingl *et al.*, 1975), Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA, 18th edition (1990)), and Principles and Practice of Ophthalmology (Albert and Jakobiec eds., W.B. Saunders Company, (1994)) for example.

The present invention concerns methods and compositions for the prophylactic and therapeutic treatment of ophthalmic disorders, and particularly posterior segment ophthalmic disorders, with a therapeutic agent. The compositions and the methods employing them have been found to unexpectedly deliver therapeutically effective amounts of the therapeutic agent to the posterior segment when administered topically to the eye of an animal. The therapeutic agent may be transported through the conjunctiva by active or facilitated transport, or by passive transport mechanisms.

The term therapeutic agent refers to any pharmaceutically acceptable salt, derivative, stereoisomer, or mixture of stereoisomers of a therapeutic agent, or to the therapeutic agent itself. Pharmaceutically acceptable salts or derivatives of therapeutic agents may also be used in the methods and compositions of the present invention. The term "pharmaceutically acceptable salt" used herein refers to those salts of the parent compound that do not significantly or adversely affect the pharmaceutical properties (*e.g.*, toxicity, efficacy, etc.) of the parent compound. Pharmaceutically acceptable salts administrable by means of the compositions of this invention include, for example, chloride, iodide, bromide, hydrochloride, acetate, nitrate, stearate, palmoate, phosphate, and sulfate salts. Exemplary techniques for producing pharmaceutically acceptable derivatives include methylation, halogenation, acetylation, esterification, and hydroxylation. Other examples also include those selected or derived from those described in U.S. Patent No. 5,917,090.

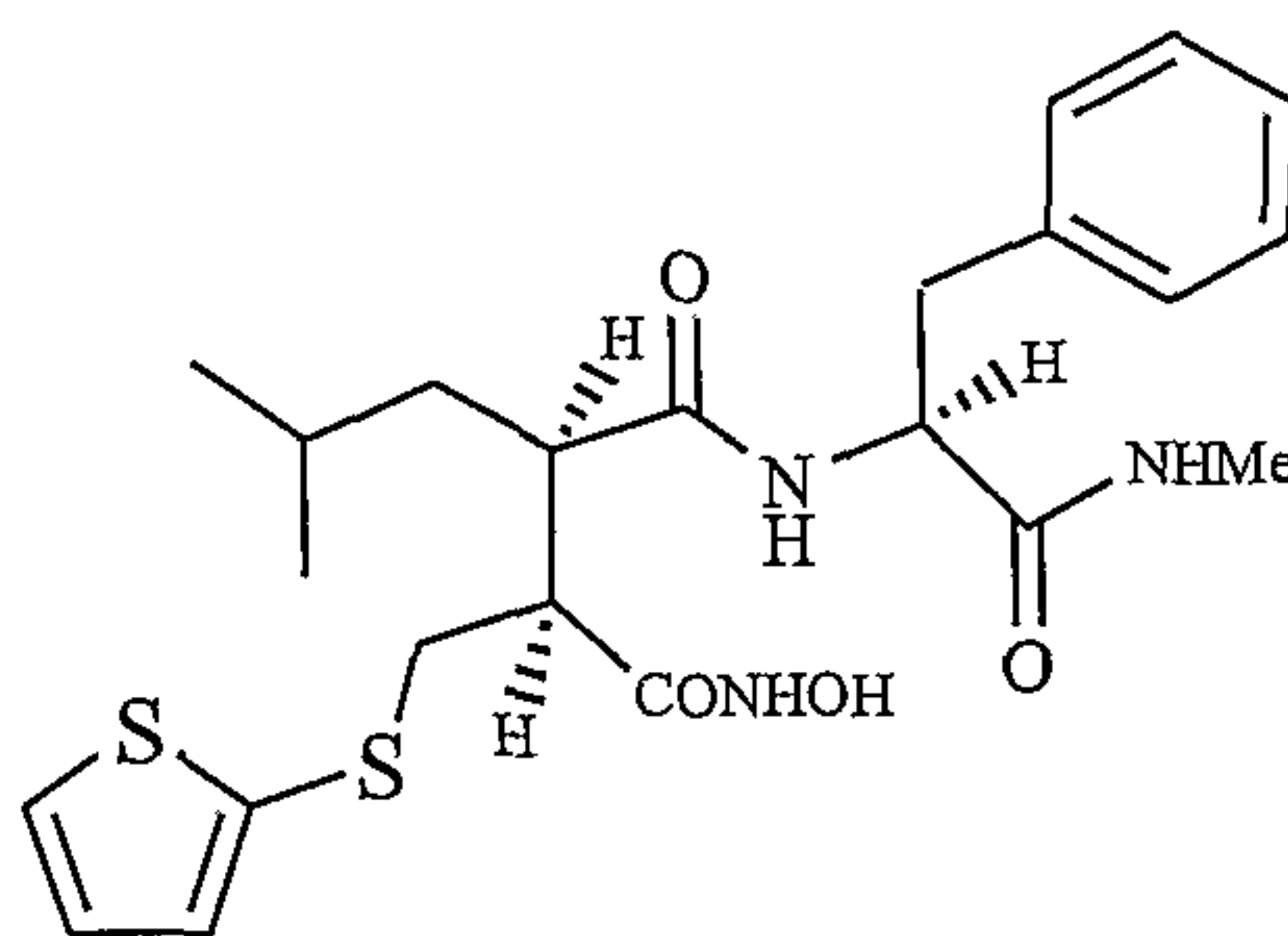
Therapeutic agents useful in the methods and compositions of the present invention include MMP inhibitors like batimastat, marimastat or AG-3340; hydroxamic acids; macrocyclic anti-succinate hydroxamate derivatives; tetracyclines; steroid inactivators of metalloproteinase translation; anti-angiogenics; DNA binding (minor groove) compounds; peptide-like therapeutic agents such as TIMPs, N-carboxyalkyl peptides, polyamines and glycosaminoglycans; non-steroidal anti-inflammatory drugs (NSAIDs); corticosteroids; immunosuppressive agents; antibiotics; receptor antagonists; RNA aptamers; anti-oxidants and antibodies.

Hydroxamic acid-based therapeutic agents are described in U.S. Patent No. 5,240,958, and preferably have the general formula:



where R^1 represents thienyl; R^2 represents a hydrogen atom or a C_1 - C_6 alkyl, C_1 - C_6 alkenyl, phenyl(C_1 - C_6) alkyl, cycloalkyl(C_1 - C_6)alkyl or cycloalkenyl(C_1 - C_6)alkyl group; R^3 represents an amino acid side chain or a C_1 - C_6 alkyl, benzyl, (C_1 - C_6 alkoxy)benzyl or benzyloxy(C_1 - C_6 alkyl) or benzyloxy benzyl group; R^4 represents a hydrogen atom or a C_1 - C_6 alkyl group; R^5 represents a hydrogen atom or a methyl group; n is an integer having the value 0, 1 or 2; and A represents a C_1 - C_6 hydrocarbon chain, optionally substituted with one or more C_1 - C_6 alkyl, phenyl or substituted phenyl groups; or a salt thereof.

Other hydroxamic acid-based therapeutic agents include phosphinamide-based hydroxamic acids, peptidyl hydroxamic acids including p-NH₂-Bz-Gly-Pro-D-Leu-D-Ala-NHOH (FN-439), hydroxamic acids with a quaternary-hydroxy group, and succinate-derived hydroxamic acids related to batimastat. See, e.g., Pikul *et al.*, *Journal of Medical Chemistry* 42(1):87-94 (1999); Odake *et al.*, *Biochem Biophys Res Commun* 199(3):1442-46 (1994); Jacobson *et al.*, *Bioorganic Medical Chemistry Letters* 8(7):837-42 (1998); Steinman *et al.*, *Bioorganic Medical Chemistry Letters* 8(16):2087-92 (1998). Macrocyclic anti-succinate hydroxamate derivatives are also effective therapeutic agents. See Cherney *et al.*, *Bioorganic Medical Chemistry Letters* 9(9):1279-84 (1999). Batimastat, also known as BB-94, is a relatively insoluble chemical having the chemical name [2- R -[1(S^*),2 R^* ,3 S^*]]- N^4 -hydroxy- N^1 -[2-(methylamino)-2-oxo-1-(phenylmethyl)ethyl]-2-(2-methylpropyl)-3-[(2-thienylthio)methyl] butanediamide or (2 S ,3 R)-5-methyl-3-[[(αS) - α -(methylcarbamoyl)phenethyl]carbamoyl]-2-[(2-thienylthio)methyl]hexanohydroxamic acid, and the formula:



Anti-angiogenics comprise a class of compounds including growth factors, cytokines and peptides, which share characteristics such as the ability to inhibit angiogenesis, endothelial cell proliferation, migration, tube formation and neovascularization. Preferred anti-angiogenics include endostatin and active collagen fragment derivatives, such as arresten (a 26 kDa NC1 domain of the alpha 1 chain of type IV collagen), thrombospondin, interleukin-12, angiostatin and active fragments and derivatives of plasminogen. See Colorado *et al.*, *Cancer Research* 60(9):2520-26 (2000); Sunamura *et al.*, *Pancreas* 20(3):227-33 (2000); Griscelli *et al.*, *Proceedings of the National Academy of Sciences U.S.A.*, 95(11):6367-72 (1998). Other preferred anti-angiogenics are growth factors such as basic fibroblast growth factor (bFGF), which may be used alone or in combination with other anti-angiogenics such as all-trans retinoic acid to stimulate native MMP inhibitors such as tissue inhibitor of metalloproteinases-1 (TIMP-1) protein. See Bigg *et al.*, *European Journal of Biochemistry* 267(13):4150-56 (2000).

Other preferred therapeutic agents include the tetracyclines, especially minocycline, doxycycline, and COL-3, and steroid inactivators of metalloproteinase translation, such as dexamethasone. See Fife *et al.*, *Cancer Letters* 153(1-2):75-8 (2000); Gilbertson-Beadling *et al.*, *Cancer Chemother. Pharmacol.* 36(5):418-24 (1995); Greenwald *et al.*, *Journal of Rheumatology* 19(6):927-38 (1992); Shapiro *et al.*, *Journal of Immunology* 146(8):2724-29 (1991). A further group of therapeutic agents includes DNA binding (minor groove) compounds such as distamycin A and its sulphonic derivatives PNU145156E and PNU153429, anthramycin, pyrrolo[2,1-c][1,4]benzodiazepine (PBD) and its methyl esters, and other polypyrrole minor groove binders. See, *e.g.*, Baraldi *et al.*, *Journal of Medical Chemistry* 42(25):5131-41 (1999); Possati *et al.*, *Clin. Exp. Metastasis* 17(7):575-82 (1999).

The peptide-like therapeutic agents comprise a varied class of compounds that includes peptides, peptide mimetics, pseudopeptides, polyamines, and glycosaminoglycans. Tissue inhibitors of metalloproteinases (TIMPs) are peptides and polypeptides that inhibit the action of metalloproteinases and that share structural characteristics such as intrachain disulfide bonds. Preferred TIMPs include recombinant and isolated forms of natural TIMPs, including TIMP-1 (a 28.5 kDa polypeptide), TIMP-2 (a 21 kDa polypeptide), and TIMP-3 (a 24-25 kDa polypeptide), and fragments thereof that retain inhibitory function. See G. Murphy *et al.*, *Biochemistry* 30(33):8097-102 (1991); A.N. Murphy *et al.*, *Journal of Cell Physiology* 157(2):351-58 (1993); Kishnani *et al.*, *Matrix Biology* 14(6):479-88 (1995).

N-carboxyalkyl peptides are a class of peptides that have been shown to act as therapeutic agents *in vivo*. Preferred N-carboxyalkyl peptides include $\text{CH}_3\text{CH}_2\text{CH}_2(\text{R,S})\text{CH}(\text{COOH})\text{-NH-Leu-Phe-Ala-NH}_2$, N-[D,L-2-isobutyl-3(N'-hydroxycarbonylamido)-propanoyl]-O-methyl-L-tyrosine methylamide, and $\text{HSCH}_2\text{CH}[\text{CH}_2\text{CH}(\text{CH}_3)_2]\text{CO-Phe-Ala-NH}_2$ (SIMP). See Fini *et al.*, *Invest. Ophthalmol. Vis. Sci.* 32(11):2997-3001 (1991); Stack *et al.*, *Arch. Biochem. Biophys.* 287(2):240-49 (1991); Wentworth *et al.*, *Invest. Ophthalmol. Vis. Sci.* 33(7):2174-79 (1992). Other peptide-like therapeutic agents include polyamines such as alpha-difluoromethylornithine, and glycosaminoglycans such as combretastatin and heparin. See Wallon *et al.*, *Mol. Carcinog.* 11(3):138-44 (1994); Dark *et al.*, *Cancer Research* 57 (10):1829-34 (1997); Lyons-Giordano *et al.*, *Exp. Cell Research* 186(1):39-46 (1990).

Peptide derivatives of MMPs having MMP inhibitory activity may also be used in the methods and compositions of the present invention. Preferred peptides are analogs, variants and derivatives of the amino acid sequences of MMP proenzymes. Particularly preferred peptides include analogs, variants and derivatives of a highly conserved peptide sequence that is found in all known MMP proenzymes, which has been alternatively reported as MRKPRCGNPDV (pro-collagenase) (SEQ ID NO:1) or MRKPRCGVPDVG (pro-stromelysin) (SEQ ID NO:2). See Hanglow *et al.*, *Agents Actions* 39 Spec. No.:C148-50 (1993); Melchiori *et al.*, *Cancer Research* 52(8):2353-56 (1992). More preferred peptides have the amino acid sequences Arg-Cys-Gly (SEQ ID NO:3), Arg-Cys-Gly-Val

(SEQ ID NO:4), Arg-Cys-Gly-Val-Pro (SEQ ID NO:5), Arg-Cys-Gly-Val-Pro-Asp (SEQ ID NO:6), and TMRKPRCGNPDVAN (SEQ ID NO:7). Other peptides include analogs, variants and derivatives of metalloproteinases, such as pyroGlu-Asn-Trp and synthetic ligands such as SCH 47890. *See Zhang et al., Proceedings of the National Academy of Sciences U.S.A.* 91:8447-51 (1994).

Sulfur-based therapeutic agents such as sulfonanilides and sulfonamides may also be used in the methods and compositions of the present invention. Preferred sulfur-based therapeutic agents include sulfonanilide nonsteroidal anti-inflammatory drugs (NSAIDs) such as nimesulide, acyclic sulfonamides, and malonyl alpha-mercaptoketones and alpha-mercaptoalcohols. *See, e.g., Bevilacqua et al., Drugs* 46 Suppl. 1:40-47 (1993); Hanessian *et al., Bioorganic Medical Chemistry Letters* 9(12):1691-96 (1999); Campbell *et al., Bioorganic Medical Chemistry Letters* 8(10):1157-62 (1998).

Non-steroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase inhibitors may also be used as therapeutic agents in the methods and compositions of the present invention. Exemplary NSAIDs include the salicylates, fenamates, indoles, phenylalkanoic acids and pyrazolones. Exemplary cyclooxygenase inhibitors include but are not limited to the derivatives of propionic acid, acetic acid, fenamic acid, biphenylcarboxylic acid and oxicams. These cyclooxygenase inhibitors may include COX-1 and/or COX-2 inhibitors. Preferred NSAIDs include aspirin, benoxaprofen, benzofenac, bucloxic acid, butibufen, carprofen, cicloprofen, cinmetacin, clidanac, clopirac, diclofenac, etodolac, fenbufen, fenclofenac, fenclorac, fenoprofen, fentiazac, flunoxaprofen, furaprofen, flurbiprofen, furobufen, furofenac, ibuprofen, ibufenac, indomethacin, indoprofen, isoxepac, ketoprofen, lactorolac, lonazolac, metiazinic, miroprofen, naproxen, oxaprozin, oxepinac, phenacetin, pirprofen, pirazolac, protizinic acid, sulindac, suprofen, tiaprofenic acid, tolmetin, and zomepirac. Preferred COX-2 inhibitors include celecoxib, rofecoxib, meloxicam, JTE-522, and HN-56249.

Another class of therapeutic agents includes compounds that antagonize receptors involved in posterior segment ophthalmic disorders, *e.g.*, vascular endothelial growth factor (VEGF) receptors. VEGF antagonists include peptides that inhibit the binding of VEGF to

its receptors, such as short disulfide-constrained peptides, and the synthetic peptide Ala-Thr-Trp-Leu-Pro-Pro-Arg (SEQ ID NO:8). See Fairbrother *et al.*, *Biochemistry* 37(51):17754-64 (1998); Binetruy-Tournaire *et al.*, *EMBO J.* 19(7):1525-33 (2000). VEGF antagonists inhibit the outgrowth of blood vessels by inhibiting the ability of VEGF to contact its receptors. This mechanism of anti-angiogenesis operates differently than the mechanism caused by the stimulation of growth factors such as bFGF, which act to inhibit angiogenesis by stimulating native inhibitors of proteases. Other VEGF antagonists may be derived from asymmetric variants of VEGF itself. See, e.g., Siemester *et al.*, *Proceedings of the National Academy of Sciences U.S.A.* 95:4625-29 (1998). Other useful therapeutic agents are RNA aptamers, which may be designed to antagonize VEGF or the closely related platelet-derived growth factor (PDGF), and may be administered coupled to polyethylene glycol or lipids. See, e.g., Floege *et al.*, *American Journal of Pathology* 154(1):169-79 (1999); Ostendorf *et al.*, *J. Clin. Invest.* 104(7):913-23 (1999); Willis *et al.*, *Bioconjug. Chem.* 9(5):573-82 (1998).

Antibodies used in the methods and compositions of the present invention may be directed toward receptors or compounds such as integrin which are involved in triggering posterior segment ophthalmic disorders. Exemplary antibodies include anti-integrins such as anti-alpha(v)beta(3) and anti-alpha(5) integrin antibodies, which may be used in combination with cyclic Arg-Gly-Asp. See Bayless *et al.*, *American Journal of Pathology* 156(5):1673-83 (2000). Other antibodies include vinblastine and DC101, a monoclonal neutralizing antibody that targets a VEGF receptor. See Klement *et al.*, *J. Clin. Invest.* 105(8):R15-24 (2000).

Two other classes of useful therapeutic agents include the immunosuppressives and antibiotics. Immunosuppressives are agents that suppress the immune system. They include all corticosteroids; alkylating agents such as busulphan, chlorambucil, cyclophosphamide, ethogulcid, mannometine, melphalan, mitobronitol, mustine, thiotepa, tretamine, and uramustine; antimetabolites such as folic acid antagonists (methotrexate), purine antagonists (mercaptopurine, azathiopurine, thioguanine), and pyrimidine antagonists (fluorouracil, cytarabine, floxuridine); alkaloids such as vincristine, vinblastine, and

demecolcine; glucosides (etoposide); cyclosporins; asparaginase; and others such as procarbazine, dacarbazine, hydroxurea, roxaxane, urethane, and cisplatin. Antibiotic therapeutic agents include tobramycin, gentamycin, fluoroquinolone derivatives including norfloxacin, ofloxacin, and ciprofloxacin, naphthyridine, tetracyclines, oxazolidinones, and macrolides like erythromycin, clarithromycin, and azithromycin.

In addition, the compositions of the invention may be enriched with one or more of the stereoisomers of a therapeutic agent, or may be substantially optically pure with respect to one stereoisomer. The methods for using therapeutic agents may also comprise enriched stereoisomers or mixtures. One skilled in the art is familiar with designing synthetic schemes that employ one or more optically pure reagents or intermediates, or stereoisomerically enriched reagents or intermediates, resulting in either a substantially optically pure composition or a stereoisomerically enriched composition. A substantially optically pure composition contains about 85 to about 95 percent, or higher, of one stereoisomer. Chromatographic, enzymatic, or selective crystallization techniques for enriching or purifying stereoisomers of therapeutic agents, mixtures of therapeutic agents, or any intermediate or reagent used to prepare a therapeutic agent may also be used.

In a preferred embodiment, the compositions of the present invention comprise a therapeutically effective amount of a therapeutic agent. Preferred concentrations of therapeutic agent(s) in the compositions of the present invention are in the range of about 0.01 to about 10 percent (wt/wt). A more preferred range of concentrations is from about 0.05 to about 5.0 percent, and even more preferred concentrations are from about 0.1 to about 1.0 percent.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, *i.e.*, healing or amelioration of chronic conditions, a reduction in: neovascularization, inflammation, atrophy or other symptoms; an increase in rate of healing of such conditions, or a detectable change in the levels of MMP, cytokine profiles, or cellular activity or other related biochemical events in the retina or surrounding tissue. When applied to an individual active ingredient, administered alone, the term refers

to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially, or simultaneously.

Therapeutic efficacy and toxicity of the compositions may be determined by standard pharmaceutical, pharmacological, and toxicological procedures in cell cultures or experimental animals. For example, numerous methods of determining ED_{50} (the dose therapeutically effective in 50 percent of the population) and LD_{50} (the dose lethal for 50 percent of the population) exist. The dose ratio between therapeutic and toxic effects is the therapeutic index, and it can be expressed as the ratio ED_{50}/LD_{50} . Compositions exhibiting high therapeutic indices are preferred. The data obtained from cell culture assays or animal studies may be used in formulating a range of dosages for human use. The dosage is preferably within a range of concentrations that includes the ED_{50} with little or no toxicity, and may vary within this range depending on the dosage form employed, sensitivity of the patient, and the route of administration.

The pH of the inventive compositions is preferably between about 5 and about 8, and may be adjusted for the particular therapeutic agent(s) used. Purified water USP and various acids and bases suitable for ophthalmic use, or combinations of acids and bases, may be used for adjusting the pH of the compositions. Non-limiting examples of acids and bases include acetic acid, boric acid, citric acid, lactic acid, phosphoric acid, hydrochloric acid, sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate, and TRIS.

The osmotic pressure of the compositions may be adjusted by methods known in the art to be between about 40 to about 400 milliosmolar (mOsM), more preferably between about 100 to about 300 mOsM. A preferred method of adjusting osmotic pressure is the addition of physiologically and ophthalmically acceptable salts. Sodium chloride, which approximates physiological fluid, is the preferred salt, for use in concentrations ranging from about 0.01 to about 1 percent by weight, or any value in that range. Preferably, the concentration is between about 0.1 to about 1 percent. Equivalent amounts of one or more salts made up of cations such as potassium, ammonium and the like and anions such as

chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate, bisulfite and the like, e.g., potassium chloride, sodium thiosulfate, sodium bisulfite, ammonium sulfate, and the like, can also be used in addition to or instead of sodium chloride to achieve osmotic pressures within the above-stated ranges.

Additional components of the composition may be chosen from any of those used in or capable of being used in a pharmaceutical formulation, especially those designed for topical administration to the eye. A non-exclusive list of components includes preservatives, stabilizers, chelating agents, dyes, antibiotics, antimicrobials, and anti-fungal agents. Preservatives such as benzalkonium chloride may be used in a range between about 0.001 to 1 percent by weight, or any value in this range. The compositions of the present invention may further comprise pharmaceutically acceptable carriers, excipients, gels, solutions, or diluents suitable for topical ophthalmic administration, and may include pharmaceutically acceptable polymeric suspension agents. Suitable carriers or excipients include, but are not limited to, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycol. Suitable techniques for the formulation and administration of the compositions of the present invention may be found in Remington's Pharmaceutical Sciences, 18th edition (1990).

In another preferred embodiment, the compositions of the present invention comprise a therapeutically effective amount of a therapeutic agent and a pharmaceutically acceptable polymeric suspension agent that is capable of increasing the residence time of the therapeutic agent in the eye. An increased residence time is desirable because it enables a greater amount of the therapeutic agent to penetrate the conjunctiva or to otherwise be transported to the posterior segment of the eye, even at relatively low concentrations of therapeutic agent. Generally, the concentration of therapeutic agent is preferred to be kept relatively low in order to avoid systemic uptake and possible side effects.

Exemplary polymeric suspension agents include dextrans, polyethylene glycols, polyvinylpyrrolidone, polysaccharide gels, Gelrite®, cellulosic polymers like hydroxypropyl methylcellulose, and carboxyl-containing polymers such as polymers or copolymers of acrylic acid, as well as other polymeric demulcents. A preferred polymeric

suspending agent is a water-swellaable, water-insoluble polymer, especially a crosslinked carboxyl-containing polymer.

Crosslinked carboxyl-containing polymers that can be used in practicing this invention are, in general, well known in the art. In a preferred embodiment, these polymers may be prepared from at least about 90 percent, and preferably from about 95 to about 99.9 percent by weight, based on the total weight of monomers present, of one or more carboxyl-containing monoethylenically unsaturated monomers. Acrylic acid is the preferred carboxyl-containing monoethylenically unsaturated monomer, but other unsaturated, polymerizable carboxyl-containing monomers, such as methacrylic acid, ethacrylic acid, β -methylacrylic acid (crotonic acid), *cis*- α -methylcrotonic acid (angelic acid), *trans*- α -methylcrotonic acid (tiglic acid), α -butylcrotonic acid, α -phenylacrylic acid, α -benzylacrylic acid, α -cyclohexylacrylic acid, β -phenylacrylic acid (cinnamic acid), coumaric acid (*o*-hydroxycinnamic acid), umbellic acid (*p*-hydroxycoumaric acid), and the like may be used in addition to or instead of acrylic acid.

The polymers may be crosslinked by a polyfunctional crosslinking agent, preferably a difunctional crosslinking agent. The amount of crosslinking should be sufficient to form insoluble polymer particles, but not so great as to unduly interfere with sustained release of the therapeutic compound. Typically the polymers are only lightly crosslinked. Preferably the crosslinking agent is contained in an amount of from about 0.01 to about 5 percent, preferably from about 0.1 to about 5.0 percent, and more preferably from about 0.2 to about 1 percent, based on the total weight of monomers present.

Suitable crosslinking agents include non-polyalkenyl polyether difunctional crosslinking monomers, such as divinyl glycol; 2,3-dihydroxyhexa-1,5-diene; 2,5-dimethyl-1,5-hexadiene; divinylbenzene; N,N-diallylacrylamide; N,N-diallylmethacrylamide, and the like. Other suitable crosslinking agents include polyalkenyl polyether crosslinking agents such as polyallyl sucrose or polyallyl pentaerythritol (*see, e.g.*, U.S. Patent No. 2,798,053), and diolefinic non-hydrophilic macromeric crosslinking agents as disclosed in U.S. Patent Nos. 4,192,827 and 4,136,250.

The crosslinked carboxyl-vinyl polymers may be made from a carboxyl-vinyl monomer or monomers as the sole monoethylenically unsaturated monomer present, together with a crosslinking agent or agents. Preferably, the polymers are ones in which up to about 40 percent, and preferably from about 0 to about 20 percent by weight, of the carboxyl-containing monoethylenically unsaturated monomer or monomers has been replaced by one or more non-carboxyl-containing monoethylenically unsaturated monomer or monomers containing only physiologically and ophthalmically innocuous substituents, including acrylic and methacrylic acid esters such as methyl methacrylate, ethyl acrylate, butyl acrylate, 2-ethylhexylacrylate, octyl methacrylate, 2-hydroxyethyl-methacrylate, 3-hydroxypropylacrylate, and the like, vinyl acetate, N-vinylpyrrolidone, as well as the monoethylenically unsaturated monomers disclosed in U.S. Patent No. 4,548,990.

Particularly preferred polymers are lightly crosslinked acrylic acid polymers wherein the crosslinking monomer is 2,3-dihydroxyhexa-1,5-diene or 2,3-dimethylhexa-1,5-diene. Preferred commercially available polymers include polycarbophil (Noveon AA-1) and Carbopol®. Most preferably, the polycarbophil-containing DuraSite® polymeric delivery system (InSite Vision, Inc., Alameda, CA), which is a sustained release topical ophthalmic delivery system that releases a drug at a controlled rate, is used as the polymeric suspension agent in the compositions of the present invention.

The crosslinked carboxyl-vinyl polymers used in practicing this invention are preferably prepared by suspension or emulsion polymerizing the monomers, using conventional free radical polymerization catalysts, to a dry particle size of not more than about 1 to 10 μm in equivalent spherical diameter; *e.g.*, to provide dry polymer particles ranging in size from about 1 to about 30 μm , and preferably from about 5 to about 20 μm , in equivalent spherical diameter. Using polymer particles that were obtained by mechanically milling larger polymer particles to this size is preferably avoided. In general, such polymers will have a molecular weight that has been variously reported as being from about 250,000 to about 5,000,000,000.

In the most preferred embodiment of the invention, the particles of crosslinked carboxyl-vinyl polymer are monodisperse, meaning that they have a particle size

distribution such that at least 80 percent of the particles fall within a 10 μm band of major particle size distribution. More preferably, at least 90 percent and most preferably at least 95 percent, of the particles fall within a 10 μm band of major particle size distribution. Also, a monodisperse particle size means that there is no more than 20 percent, preferably no more than 10 percent, and most preferably no more than 5 percent particles of a size below 1 μm . The use of a monodispersion of particles will give maximum viscosity and an increased eye residence time of the ophthalmic medicament delivery system for a given particle size. Monodisperse particles having a particle size of 30 μm and below are most preferred. Good particle packing is aided by a narrow particle size distribution.

The compositions of the present invention normally contain 0.01 to 10 percent, preferably 0.05 to 5.0 percent, more preferably 0.1 to 1.03 percent, of the therapeutic agent, and 0.1 to 10 percent, preferably 0.5 to 6.5 percent, of a polymeric suspension agent. In the case of the above described water-insoluble, water-swellaable crosslinked carboxyl-vinyl polymer, a more preferred amount of the polymeric suspending agent is an amount ranging from about 0.5 to about 2.0 percent, or any chosen range between these percentages. Especially preferred embodiments comprise from about 0.5 percent to about 1.3 percent polymer, and in certain embodiments from about 0.6 to about 0.9 percent, based on the weight of the composition. Although referred to in the singular, it should be understood that one or more species of polymeric suspension agent, such as the crosslinked carboxyl-containing polymer, may be used with the total amount falling within the stated ranges. In one preferred embodiment, the composition contains from about 0.5 to about 2.0 percent, or any chosen range between these percentages, of a polycarbophil, such as NOVEON AA-1, and even more preferred is from about 0.60 to about 1.3 percent.

In one embodiment, the amount of insoluble lightly crosslinked carboxyl-vinyl polymer particles, the pH, and the osmotic pressure can be correlated with each other and with the degree of crosslinking to give a composition having a viscosity in the range of from about 500 to about 100,000 centipoise, and preferably from about 1,000 to about 30,000 or about 1,000 to about 10,000 centipoise, as measured at room temperature (about 25° C) using a Brookfield Digital LVT Viscometer equipped with a number 25 spindle and a 13R

small sample adapter at 12 rpm. Alternatively, when the viscosity is within the range of 500 to 3000 centipoise, it may be determined by a Brookfield Model DV-11+, choosing a number cp-52 spindle at 6 rpm. One skilled in the art is familiar with methods for adjusting and optimizing viscosity ranges for pharmaceutical compositions. When water soluble polymers such as hydroxypropyl methylcellulose (HPMC) are used as suspension agents, the viscosity will typically be about 10 to about 400 centipoise, more typically about 10 to about 200 centipoises or about 10 to about 25 centipoise.

Also provided are methods for prophylactic and therapeutic treatment of diseases and conditions manifesting or associated with the posterior segment of the eye comprising administering a topical ophthalmic composition of the present invention to an animal in need of such treatment. Another method provided is a method for identifying or selecting a topical ophthalmic composition for administering a therapeutic agent. The method comprises selecting a therapeutic agent, selecting a polymer-type carrier or polymeric suspension agent, and detecting the occurrence of a meaningful patient benefit, e.g., the inhibition of proteinase activity in the posterior segment.

The duration of prophylactic and therapeutic treatment will vary depending on the particular disease or condition being treated. Some diseases lend themselves to acute treatment whereas others require long-term therapy. For example, proliferative retinopathy can reach a threshold in a matter of days as seen in ROP, some cases of diabetic retinopathy, and neovascular glaucoma. Premature infants are at risk for neovascularization around what would be 35 weeks gestation, a few weeks after birth, and will remain at risk for a short period of time until the retina becomes vascularized. Diabetic retinopathy can be acute but may also remain in the proliferative phase for a longer period of time. Diabetic retinopathy will eventually become quiescent as the vasoproliferative signal diminishes due to neovascularization and destruction of the retina.

Application of the teachings of the present invention to a specific problem or environment is within the capabilities of one having ordinary skill in the art in light of the teachings contained herein. Examples of the products and processes of the present invention appear in the following examples.

EXAMPLE 1**Preparation of Compositions Containing a Therapeutic Agent**

Various formulations of the compositions of the present invention were compounded, and are listed in the following tables.

Compound	Formulation 1 (w/w%) ¹	Formulation 2 (w/w%) ¹	Formulation 3 (w/w%) ¹
HPMC	2.5		
Therapeutic Agent	0.3	0.3	0.3
Mannitol			1.0
Sorbitol	1.5		
Glycerin	1.0		
Poloxamer 407	0.5	0.05	0.05
Polycarbophil		1.25	0.85
NaCl		0.6	0.2
Sodium Citrate Dihydrate		0.35	0.35
Benzalkonium Chloride (BAK)			0.008
EDTA		0.1	0.1
Water	q.s. to 100%	q.s. to 100%	q.s. to 100%
NaOH	q.s. to pH 6	q.s. to pH 6	q.s. to pH 6

1. The therapeutic agent in Formulations 1-3 is batimastat.

Compound	Formulation 4 (w/w%) ²	Formulation 5 (w/w%) ³	Formulation 6 (w/w%) ⁴
HPMC	2.5		
Therapeutic Agent	0.01	0.1	1.0
Mannitol			1.0
Sorbitol	1.5		
Glycerin	1.0		
Poloxamer 407	0.5	0.05	0.05
Polycarbophil		1.25	0.85
NaCl		0.6	0.2
Sodium Citrate Dihydrate		0.35	0.35
Benzalkonium Chloride (BAK)			0.008
EDTA		0.1	0.1
Water	q.s. to 100%	q.s. to 100%	q.s. to 100%
NaOH	q.s. to pH 6	q.s. to pH 6	q.s. to pH 6

2. The therapeutic agent in Formulation 4 is arresten.
3. The therapeutic agent in Formulation 5 is nimesulide.
4. The therapeutic agent in Formulation 6 is doxycycline.

The physical and chemical characteristics of the compositions of the invention may be modified or optimized according to the skill in the art. Thus, pH, osmotic pressure, viscosity, and the content of various additional components may be chosen from any appropriate range known or modified from the examples given here. The methods for preparing and selecting exemplary formulations containing polymeric suspension agents are described in U.S. Patent Nos. 5,188,826 and 5,192,535, for example. In general, the pharmaceutical compositions of the invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, emulsifying, encapsulating, entrapping, or lyophilizing processes.

The compositions may be formulated in any of several ways. For example, the lightly-crosslinked polymer particles, the therapeutic agent, the osmotic pressure-adjusting salt and any of the optional ingredients also being used may be pre-blended, added to all or part of the water, and stirred vigorously until apparent polymer dispersion is complete, as evidenced by the absence of visible polymer aggregates, which usually occurs within about an hour. Sufficient pH adjusting agent is then added incrementally to reach the desired pH, and more water to reach 100 percent formula weight can be added at this time, if necessary.

Another convenient method involves adding the therapeutic agent to about 95 percent of the final water volume and stirring for a sufficient time to saturate the solution. Solution saturation can be determined in a known manner, *e.g.*, using a spectrophotometer. The lightly crosslinked polymer particles and the osmotic pressure-adjusting salt are first blended in dry form and then added to the drug-saturated suspension and stirred until apparent polymer hydration is complete. Following the incremental addition of sufficient pH adjusting agent to reach the desired pH, the remained of the water is added, with stirring, to bring the composition to 100 percent formula weight.

A preferred method of formulating the topical ophthalmic compositions of this invention involves adding the polymer to 90 grams of water per 100 grams of gel, then stirring for about 1 hour until the gel is fully hydrated. The therapeutic agent is then added as an aqueous solution or a suspension, with stirring. Next, sodium chloride is added as a

solid, together with sufficient water to bring the mass to 100 grams, and the pH is adjusted to the final pH, *e.g.*, with 10N sodium hydroxide.

The prepared composition is then sterilized, preferably by briefly heating, *e.g.*, for about 30 minutes with steam at about 121 degrees Celsius, and then filled into appropriate containers. Alternatively, the formulation may be sterilized by dissolving the drug in an appropriate solvent, sterile filtering and precipitating the drug in the formulation. Preservative-free compositions may be filled into unit-dose containers, at the preferred viscosity, eliminating the potential for preservative-related irritation and sensitization of the corneal epithelium, as has been observed to occur particularly from ophthalmic medicaments containing preservatives such as mercurial preservatives.

Compositions containing preservatives may also be filled into multiple-dose containers at the preferred viscosity, if desired, particularly because the viscosities of the compositions of this invention permit constant, accurate dosages to be administered dropwise to the eye as many times each day as necessary. In those compositions where preservatives are to be included, suitable preservatives include benzalkonium chloride in amounts ranging from about 0.001 to about 0.02 percent, chlorobutanol, preferably at about 0.5 percent, chlorobutanol chloral derivative, preferably at about 0.5 percent, methyl paraben and propyl paraben, preferably about 0.01 to about 0.05 percent, sorbic acid, preferably about 0.2 percent, Cetrimide, preferably about 0.01 percent, polyquat, preferably about 0.001 percent, cetyl bromide, preferably about 0.01 percent, and the like, each of the foregoing preservative amounts being based on the total weight of the composition.

EXAMPLE 2

Topical Ophthalmic Administration of a Composition Containing a Therapeutic Agent in Mice

A newborn mouse animal model of retinopathy of prematurity, which may be used as a model of retinal neovascularization conditions and diseases such as diabetic retinopathy and oxygen-induced blindness, demonstrates the utility and surprisingly advantageous topical ophthalmic administration of a therapeutic agent to the posterior segment of the eye.

Newborn mice on postnatal day 7 are kept in high oxygen (75 percent) from day 7 to 11, and then are brought to normal room air on day 12. A relative hyperoxia results, and retinal neovascularization is seen in 100 percent of the exposed animals by day 17. Some of the animals (n = 9) initially exposed to the oxygen cycle receive Formulation 1 eyedrops four times a day in the right eye on days 14-17 (four days) (Group I). Some animals (n = 9) receive the same eyedrops, administered similarly, on days 13-17. In another group of animals (n = 9) (Group III), the eyedrops are instilled in the right eye and normal saline is instilled in the left eye (control). Animals are sacrificed on day 17. Newborn animals kept in room air only for 17 days may serve as controls.

Eye tissue is processed for paraffin embedding sections, which are stained for nuclei with DAPI (diamidinophenylindole). Sections can be examined under a fluorescence microscope and nuclei on the vitreous side of the inner limiting membrane of the retina, representing microvascular cells, are counted in each section using a masked protocol.

Numerous neovascular tufts may be seen protruding from the retina into the vitreous in animals exposed to hyperoxia (75 percent oxygen) followed by room air. Quantification reveals about 52.86 neovascular nuclei per section in experimental animals (without drug treatment) compared to controls (0.53 neovascular nuclei per section). Animals treated with Formulation 1 eyedrops show a decrease in neovascular nuclei by 27.8 percent (Group I), 38.3 percent (Group II) and 39.47 percent (Group III) respectively (Fig. 1).

Analysis of MMP-2 activity in animals with retinal neovascularization shows a significant increase in the pro-form of MMP-2 (72 kDa) compared to controls (Fig. 2). The active form of MMP-2 (62 kDa), which is undetectable in controls, is also significantly increased in animals with neovascularization. The Formulation 1 eyedrops decrease the activity of both pro- and active forms of MMP-2. Analysis of MMP-9 activity in animals with retinal neovascularization shows a significant increase in the pro-form of MMP-9 (92 kDa) compared to controls (Fig. 3). The active form of MMP-9 (84 kDa), which is undetectable in controls, is significantly increased in animals with retinal neovascularization. Treatment with Formulation 1 eyedrops decreases the activity of both

pro- and active forms of MMP-9 significantly. Animals with retinal neovascularization also show a significant increase in both the 32 kD and 54 kD molecular weight forms of urokinase compared to controls. Zymographic analysis does not show any change in activity of either form of urokinase in animals treated with Formulation 1 eyedrops (Fig. 4).

In another study, animals are treated with hyperoxia conditions, as described above. Then, batimastat is introduced into the animals *via* intraperitoneal injection (IP). A course of IP injection on days 12, 14 and 16 results in a 72 percent reduction in neovascularization in the same animal model (Das *et al.*, Archives of Ophthalmology, 117:498-503 (1999)).

The result of Formulation 1 eyedrop formulation on the inhibition of retinal neovascularization is significant and the effect is specific to MMP inhibition, as shown by zymographic analysis and urokinase assays (Fig. 4). These results also show that the drug effectively reaches the retinal tissue and, thus, can be used to treat the retina *via* topical delivery.

EXAMPLE 3

Topical Ophthalmic Administration of a Composition Containing a Therapeutic Agent in Rabbits

A study in rabbits will examine the ^{14}C activity in ocular tissues and blood plasma following administration of a topical ophthalmic composition containing 0.3 percent labeled therapeutic agent (batimastat) in the DuraSite® delivery vehicle. The ocular tissues to be examined are the aqueous humor, cornea, iris and ciliary body, vitreous humor, retina and choroid, and the sclera. The study will proceed in three step-wise phases: phase 1 will examine ^{14}C activity at 20 minutes, 40 minutes, 1 hour and 2 hours post-administration, phase 2 will examine ^{14}C activity at 3 and 4 hours post-administration, and phase 3 will examine ^{14}C activity at 6 and 8 hours post-administration. Initially, 6 rabbits (12 eyes) will be examined at each time point. If any phase of the study is not executed, the rabbits allocated to that phase may be reassigned to other time points to better estimate bioavailability and pharmacokinetics. Nor more than 12 rabbits will be assigned to any single time point. It is anticipated that 48-54 total rabbits will be used in the study. To control bias, animals will be randomly enrolled in the study. Within an animal room (total

capacity 54 rabbits), each rabbit eligible for enrollment in the study will be randomly assigned a temporary sequential number. Rabbits will then be selected for use in the study in sequential order of temporary number.

This study will use 48-54 female New Zealand White rabbits that weigh approximately 1.8 to 2.8 kg upon arrival and will be approximately 9 weeks old. Each rabbit will be identified with an ear tag bearing a unique number, and the rabbit's cage will also bear the same number. Rabbits will be acclimated to the laboratory environment in a specified quarantine area for a minimum of two weeks before being used in the study. Rabbits will receive a daily ration of commercially available feed and tap water *ad libitum*. Rabbit health will be monitored daily. Rabbits will be placed in temporary housing after instillation of ^{14}C -labeled test material. The rabbits will be anesthetized and euthanized at the conclusion of the *in vivo* experimental period.

The test material will be administered with a positive displacement micropipettor. The average mass and standard deviation of dispensed test material will be estimated. Approximately 25 mg of test material will be instilled into the lower cul-de-sac of both eyes. The material will be placed into the eye by gently pulling the lower lid away from the globe to form a cup into which the material will be instilled.

Rabbits will be anesthetized with an intramuscular injection of ketamine and xylazine (0.4ml/kg each) approximately 20 minutes prior to the scheduled collection time of aqueous humor. Aqueous humor will be collected from both eyes according to methods known in the art. Aqueous humor will be collected from OD, then OS. A 0.5 ml syringe with a fixed 28G x ½" needle will be used, and an ophthalmic solution of 0.5 percent proparacaine hydrochloride will be administered prophylactically to all eyes without testing for corneal reflex. Eyes will be irrigated with commercially available Eye Irrigating Solution. Both eyes will be enucleated starting with OD. Tissues collected will include: bulbar conjunctiva, cornea, iris, sclera, vitreous humor, and retina. Tissues will be placed into preweighed scintillation vials. All scintillation vials will be capped and weighed. Immediately after the aqueous humor has been collected from both eyes, approximately 5

ml of blood will be withdrawn by intracardiac puncture. Blood will be collected into a heparinized tube.

For the bulbar conjunctiva, cornea, iris, sclera and retina/choroid, 100 μ l of reverse osmosis (RO) purified water will be added to each sample and the sample vortexed. 250 μ l of hyamine hydroxide will be added to each vial and the sample again vortexed. The samples will then be incubated at 55 degrees Celsius in a water bath until solubilized (approximately 1-4 hours). After solubilization is complete, the samples will again be vortexed, and 6 ml of CytoScintES® scintillation cocktail will be added to each sample. Solubilized samples will be immediately mixed with the scintillation cocktail by repeatedly inverting the capped vial. Vigorous shaking will be avoided.

For the vitreous humor, 100 μ l of reverse osmosis (RO) purified water will be added to each sample and the sample vortexed. 750 μ l of hyamine hydroxide will be added to each vial and the sample again vortexed. The samples will then be incubated at 55 degrees Celsius in a water bath until solubilized. After solubilization is complete, the samples will again be vortexed, and approximately 18 ml of CytoScintES® scintillation cocktail will be added to each sample. Solubilized samples will be immediately mixed with the scintillation cocktail by repeatedly inverting the capped vial. Vigorous shaking will be avoided.

For the aqueous humor, 6 ml of CytoScintES® scintillation cocktail will be added directly to each aqueous humor sample and mixed by repeatedly inverting the capped vial. There is not need to solubilize the aqueous humor sample. Blood samples will be kept in a cooler containing ice packs to keep them cold until separation. Plasma will be separated from the red blood cells by centrifugation at 4 degrees Celsius and 1200-1500g for 15 minutes. Immediately after centrifuging, 1 ml of the plasma will be pipetted from the tube and placed into a 20 ml scintillation vial. 18 ml of CytoScintES® scintillation cocktail will be added directly to each plasma sample and mixed by repeatedly inverting the capped vial. All samples will be dark-adapted overnight before counting in a Beckman LS 3801.

The topical batimastat composition reaches the retinal tissue shortly after topical administration to the eye, and is maintained in the retinal tissue at therapeutically effective

levels for at least 8 hours, as shown in Fig. 5. These results show that the drug effectively reaches the retinal tissue and thus can be used to treat the retina via topical delivery.

All publications and patents mentioned in the above specification are herein incorporated by reference. The above description, drawings and examples are only illustrative of preferred embodiments which achieve the objects, features and advantages of the present invention. It is not intended that the present invention be limited to the illustrative embodiments. Any modification of the present invention which comes within the spirit and scope of the following claims should be considered part of the present invention.

Sequence Listing

<110> Si, Erwin Chin-Chut
Bowman, Lyle M.
Rowe-Rendleman, Cheryl
Roy, Samir

<120> Methods and Compositions for Treating and Preventing Posterior
Segment
Ophthalmic Disorders

<130> 13587.001

<150> US 09/523,102

<151> 2000-03-10

<150> US 09/648,446

<151> 2000-08-28

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WO 01/68053

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 (VEGF)

WO 01/68053

PCT/US01/07171

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What is claimed is:

1. A method for treating ophthalmic disorders in a mammal in need of such treatment, comprising topically administering to the eye a composition capable of delivering a therapeutically effective amount of a therapeutic agent to the posterior segment of the eye.
2. The method of 1, wherein the mammal is a human.
3. A method for preventing ophthalmic disorders in a mammal susceptible to developing such disorders, comprising topically administering to the eye a composition capable of delivering a therapeutically effective amount of a therapeutic agent to the posterior segment of the eye.
4. The method of 3, wherein the mammal is a human.
5. A method for treating posterior segment ophthalmic disorders in a mammal in need of such treatment, comprising topically administering to the eye a composition capable of delivering a therapeutically effective amount of a therapeutic agent to the posterior segment of the eye, wherein said composition comprises a polymeric suspension agent and a therapeutic agent.
6. The method of 5, wherein the mammal is a human.
7. The method of 5, wherein the polymeric suspension agent comprises a polymer.
8. The method of 5, wherein the polymeric suspension agent comprises polycarbophil.
9. The method of 8, wherein the polycarbophil is present at a concentration of about 0.5 to about 1.5 percent by weight.
10. The method of 5, wherein the therapeutic agent is a hydroxamic acid.
11. The method of 5, wherein the therapeutic agent is an MMP inhibitor.

12. The method of 5, wherein the therapeutic agent is a macrocyclic anti-succinate hydroxamate derivative.
13. The method of 5, wherein the therapeutic agent is an anti-angiogenic.
14. The method of 5, wherein the therapeutic agent is a tetracycline.
15. The method of 5, wherein the therapeutic agent is a steroid inactivator of metalloproteinase translation.
16. The method of 5, wherein the therapeutic agent is a DNA binding compound.
17. The method of 5, wherein the therapeutic agent is a tissue inhibitor of metalloproteinase protein.
18. The method of 5, wherein the therapeutic agent is an N-carboxyalkyl peptide.
19. The method of 5, wherein the therapeutic agent is a polyamine.
20. The method of 5, wherein the therapeutic agent is a glycosaminoglycan.
21. The method of 5, wherein the therapeutic agent is a peptide consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NOs:3-8.
22. The method of 5, wherein the therapeutic agent is an NSAID.
23. The method of 5, wherein the therapeutic agent is a corticosteroid.
24. The method of 5, wherein the therapeutic agent is an antibiotic.
25. The method of 5, wherein the therapeutic agent is an immunosuppressive.
26. The method of 5, wherein the therapeutic agent is a VEGF antagonist.
27. The method of 5, wherein the therapeutic agent is an RNA aptamer.
28. The method of 5, wherein the therapeutic agent is an antibody.
29. A method for preventing posterior segment ophthalmic disorders in a mammal susceptible to developing such disorders, comprising topically administering to the eye a

- composition capable of delivering a therapeutically effective amount of a therapeutic agent to the posterior segment of the eye, wherein said composition comprises a polymeric suspension agent and a therapeutic agent.
30. A method for treating ophthalmic disorders in a mammal in need of such treatment, comprising administering topically to the eye a composition comprising a therapeutic agent and a polymeric suspension agent, wherein said composition is capable of delivering to the posterior segment of the eye a therapeutically effective amount of the therapeutic agent.
31. A method for preventing ophthalmic disorders in a mammal susceptible to developing such disorders, comprising administering topically to the eye a composition comprising a therapeutic agent and a polymeric suspension agent, wherein said composition is capable of delivering to the posterior segment of the eye a therapeutically effective amount of the therapeutic agent.
32. An ophthalmic composition for use in treating or preventing posterior segment ophthalmic disorders in a mammal by topical administration to the eye, comprising a therapeutically effective amount of a therapeutic agent and a polymeric suspension agent.
33. The composition of 32, wherein the polymeric suspension agent comprises a polymer.
34. The composition of 32, wherein the polymeric suspension agent comprises polycarbophil.
35. The composition of 34, wherein the polycarbophil is present at a concentration of about 0.5 to about 1.5 percent by weight.
36. The composition of 32, wherein the therapeutic agent is a hydroxamic acid.
37. The composition of 32, wherein the therapeutic agent is an MMP inhibitor.
38. The composition of 32, wherein the therapeutic agent is a macrocyclic anti-succinate hydroxamate derivative.
39. The composition of 32, wherein the therapeutic agent is an anti-angiogenic.

40. The composition of 32, wherein the therapeutic agent is a tetracycline.
41. The composition of 32, wherein the therapeutic agent is a steroid inactivator of metalloproteinase translation.
42. The composition of 32, wherein the therapeutic agent is a DNA binding compound.
43. The composition of 32, wherein the therapeutic agent is a tissue inhibitor of metalloproteinase protein.
44. The composition of 32, wherein the therapeutic agent is an N-carboxyalkyl peptide.
45. The composition of 32, wherein the therapeutic agent is a polyamine.
46. The composition of 32, wherein the therapeutic agent is a glycosaminoglycan.
47. The composition of 32, wherein the therapeutic agent is a peptide consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NOs:3-8.
48. The composition of 32, wherein the therapeutic agent is an NSAID.
49. The composition of 32, wherein the therapeutic agent is a corticosteroid.
50. The composition of 32, wherein the therapeutic agent is an immunosuppressive.
51. The composition of 32, wherein the therapeutic agent is an antibiotic.
52. The composition of 32, wherein the therapeutic agent is a VEGF antagonist.
53. The composition of 32, wherein the therapeutic agent is an RNA aptamer.
54. The composition of 32, wherein the therapeutic agent is an antibody.
55. A topical ophthalmic composition for use in treating or preventing posterior segment ophthalmic disorders in a mammal, comprising a therapeutic agent, wherein said composition is capable of delivering a therapeutically effective amount of the therapeutic agent to the posterior segment of the eye.

56. A topical ophthalmic composition for use in treating or preventing posterior segment ophthalmic disorders in a mammal, comprising a therapeutic agent and a polymeric suspension agent, wherein said composition is capable of delivering a therapeutically effective amount of the therapeutic agent to the posterior segment of the eye.
57. A method for treating retinal neovascularization in a mammal in need of such treatment, comprising topically administering to the eye a composition capable of delivering a therapeutically effective amount of a batimastat compound to the retina, wherein the composition comprises a polymeric suspension agent and about 0.01 to about 3 percent, by weight, of the batimastat compound.
58. The method of 57, wherein the mammal is a human.
59. The method of 57, wherein the batimastat compound is batimastat.
60. The method of 57, wherein the polymeric suspension agent comprises a polymer.
61. The method of 57, wherein the polymeric suspension agent comprises polycarbophil.
62. The method of 61, wherein the polycarbophil is present at a concentration of about 0.5 to about 1.5 percent by weight.
63. A method for preventing retinal neovascularization in a mammal susceptible to developing retinal neovascularization, comprising topically administering to the eye a composition capable of delivering a therapeutically effective amount of a batimastat compound to the retina, wherein the composition comprises a polymeric suspension agent and about 0.01 to about 3 percent, by weight, of the batimastat compound.
64. The method of 63, wherein the mammal is a human.
65. The method of 63, wherein the batimastat compound is batimastat.
66. The method of 63, wherein the polymeric suspension agent comprises a polymer.
67. The method of 63, wherein the polymeric suspension agent comprises polycarbophil.

68. The method of 67, wherein the polycarbophil is present at a concentration of about 0.5 to about 1.5 percent by weight.
69. A method for treating retinal neovascularization in a mammal in need of such treatment, comprising topically administering to the eye a composition capable of delivering a therapeutically effective amount of a batimastat compound to the retina.
70. A method for preventing retinal neovascularization in a mammal susceptible to developing retinal neovascularization, comprising topically administering to the eye a composition capable of delivering a therapeutically effective amount of a batimastat compound to the retina.
71. A method of treating retinal neovascularization in a mammal in need of such treatment, comprising administering topically to the eye a composition comprising a batimastat compound and a polymeric suspension agent, wherein said composition is capable of delivering to the retina a therapeutically effective amount of the batimastat compound.
72. The method of 72, wherein the mammal is a human.
73. The method of 72, wherein the batimastat compound is batimastat.
74. The method of 72, wherein the batimastat compound is present at a concentration of about 0.01 to about 3 percent by weight.
75. The method of 72, wherein the batimastat compound is present at a concentration of about 0.05 to about 0.5 percent by weight.
76. The method of 72, wherein the polymeric suspension agent comprises a polymer.
77. The method of 72, wherein the polymeric suspension agent comprises polycarbophil.
78. The method of 77, wherein the polycarbophil is present at a concentration of about 0.5 to about 1.5 percent by weight.
79. A method for preventing retinal neovascularization in a mammal susceptible to developing retinal neovascularization, comprising administering topically to the eye a composition comprising a batimastat compound, and a polymeric suspension agent,

wherein said composition is capable of delivering to the retina a therapeutically effective amount of the batimastat compound.

80. The method of 79, wherein the mammal is a human.
81. The method of 79, wherein the batimastat compound is batimastat.
82. The method of 79, wherein the batimastat compound is present at a concentration of about 0.01 to about 3 percent by weight.
83. The method of 79, wherein the batimastat compound is present at a concentration of about 0.05 to about 0.5 percent by weight.
84. The method of 79, wherein the polymeric suspension agent comprises a polymer.
85. The method of 79, wherein the polymeric suspension agent comprises polycarbophil.
86. The method of 85, wherein the polycarbophil is present at a concentration of about 0.5 to about 1.5 percent by weight.
87. A method for treating retinal neovascularization in a mammal in need of such treatment, comprising administering topically to the eye a composition comprising a batimastat compound, and delivering to the retina a therapeutically effective amount of the batimastat compound.
88. A method for preventing retinal neovascularization in a mammal susceptible to developing retinal neovascularization, comprising administering topically to the eye a composition comprising a batimastat compound, and delivering to the retina a therapeutically effective amount of the batimastat compound.
89. A method for treating retinal neovascularization in a mammal in need of such treatment, comprising topically administering to the eye a composition capable of delivering a therapeutically effective amount of a batimastat compound to the retina, wherein the composition comprises a carboxyl-vinyl polymeric suspension agent and about 0.01 to about 3 percent, by weight, of the batimastat compound.
90. The method of 89, wherein the mammal is a human.

91. The method of 89, wherein the batimastat compound is batimastat.
92. The method of 89, wherein the batimastat compound is present at a concentration of about 0.05 to about 0.5 percent by weight.
93. The method of 89, wherein the batimastat compound is present at a concentration of about 0.1 to about 0.3 percent by weight.
94. A method for preventing retinal neovascularization in a mammal susceptible to developing retinal neovascularization, comprising topically administering to the eye a composition capable of delivering a therapeutically effective amount of a batimastat compound to the retina, wherein the composition comprises a carboxyl-vinyl polymeric suspension agent and about 0.01 to about 3 percent, by weight, of the batimastat compound.
95. The method of 94, wherein the mammal is a human.
96. The method of 94 wherein the batimastat compound is batimastat.
97. The method of 94 wherein the batimastat compound is present at a concentration of about 0.05 to about 0.5 percent by weight.
98. The method of 94 wherein the batimastat compound is present at a concentration of about 0.1 to about 0.3 percent by weight.
99. An ophthalmic composition for use in treating or preventing retinal neovascularization in a mammal by topical administration to the eye, comprising a therapeutically effective amount of a batimastat compound.
100. An ophthalmic composition for use in treating or preventing retinal neovascularization in a mammal by topical administration to the eye, comprising a therapeutically effective amount of a batimastat compound, and a polymeric suspension agent.
101. The composition of 100, wherein the batimastat compound is batimastat.
102. The composition of 100, wherein the batimastat compound is a batimastat salt.

103. The composition of 100, wherein the batimastat compound is present at a concentration of about 0.01 to about 3 percent by weight.
104. The composition of 100, wherein the batimastat compound is present at a concentration of about 0.05 to about 0.5 percent by weight.
105. The composition of 100, wherein the batimastat compound is present at a concentration of about 0.1 to about 0.3 percent by weight.
106. The composition of 100, further comprising a second batimastat compound.
107. The composition of 100, wherein the polymeric suspension agent comprises a polymer.
108. The composition of 100, wherein the polymeric suspension agent comprises polycarbophil.
109. The composition of 108, wherein the polycarbophil is present at a concentration of about 0.5 to about 1.5 percent by weight.
110. A topical ophthalmic composition for use in treating or preventing retinal neovascularization in a mammal, comprising a batimastat compound and a polymeric suspension agent, wherein said composition is capable of delivering a therapeutically effective amount of the batimastat compound to the retina.
111. The composition of 110, wherein the batimastat compound is batimastat.
112. The composition of 110, wherein the batimastat compound is a batimastat salt.
113. The composition of 110, wherein the batimastat compound is present at a concentration of about 0.01 to about 3 percent by weight.
114. The composition of 110, wherein the batimastat compound is present at a concentration of about 0.05 to about 0.5 percent by weight.
115. The composition of 110, wherein the batimastat compound is present at a concentration of about 0.1 to about 0.3 percent by weight.

116. The composition of 110, further comprising a second batimastat compound.
117. The composition of 110, wherein the polymeric suspension agent comprises a polymer.
118. The composition of 110, wherein the polymeric suspension agent comprises polycarbophil.
119. The composition of 118, wherein the polycarbophil is present at a concentration of about 0.5 to about 1.5 percent by weight.
120. A method of treating or preventing retinal neovascularization in a mammal, comprising topically administering a composition of claim 110 to an eye of a mammal.
121. A topical ophthalmic composition for use in treating or preventing retinal neovascularization in a mammal, comprising about 0.1 to about 0.3 percent by weight of batimastat and about 0.5 to about 1.25 percent by weight of a polymeric suspension agent, wherein said composition is capable of delivering a therapeutically effective amount of batimastat to the retina.
122. A topical ophthalmic composition for use in treating or preventing retinal neovascularization in a human, comprising about 0.1 to about 0.3 percent by weight of batimastat and about 0.5 to about 1.5 percent by weight of a polycarbophil, wherein said composition is capable of delivering a therapeutically effective amount of batimastat to the retina.

Figure 1

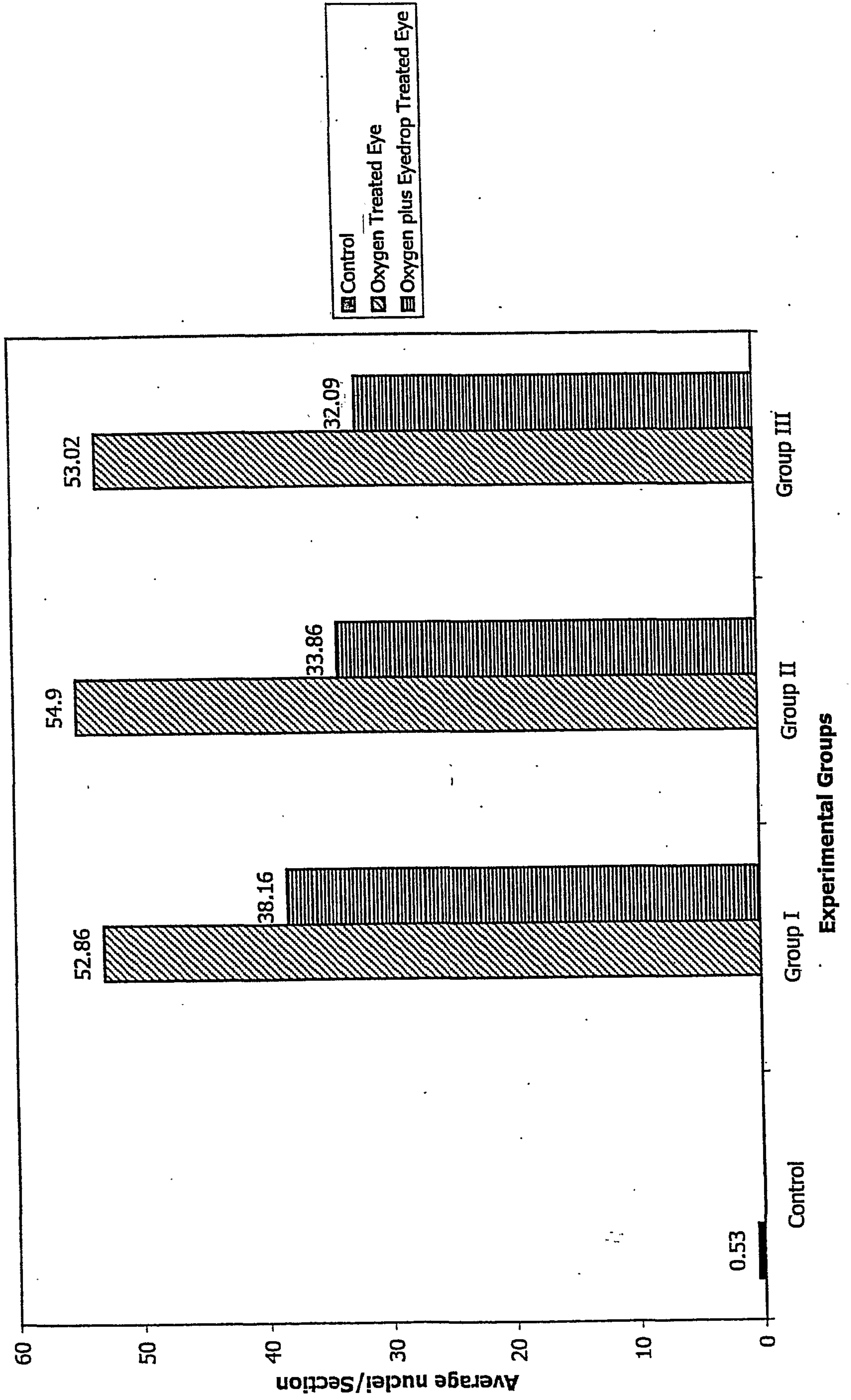


Figure 2

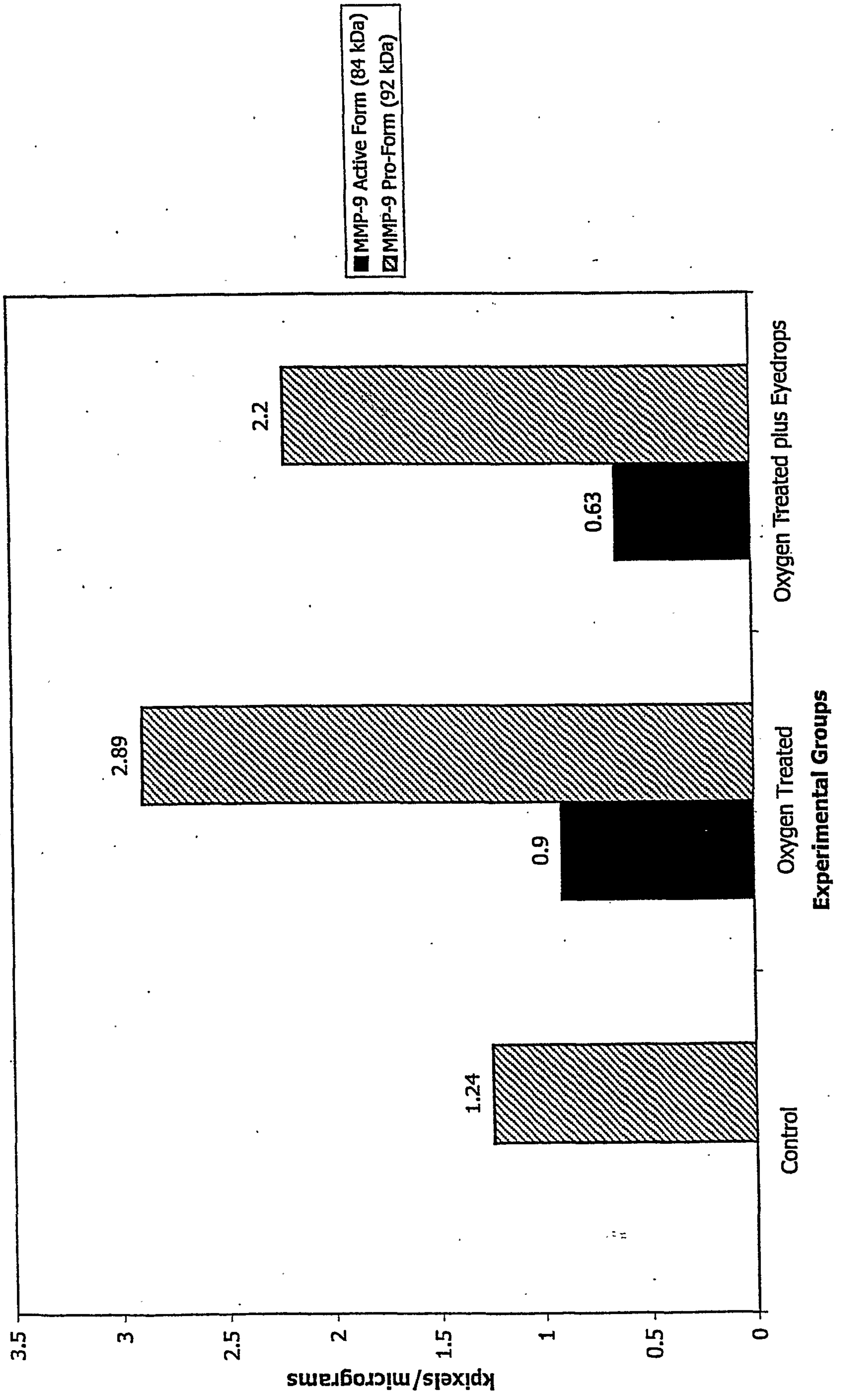


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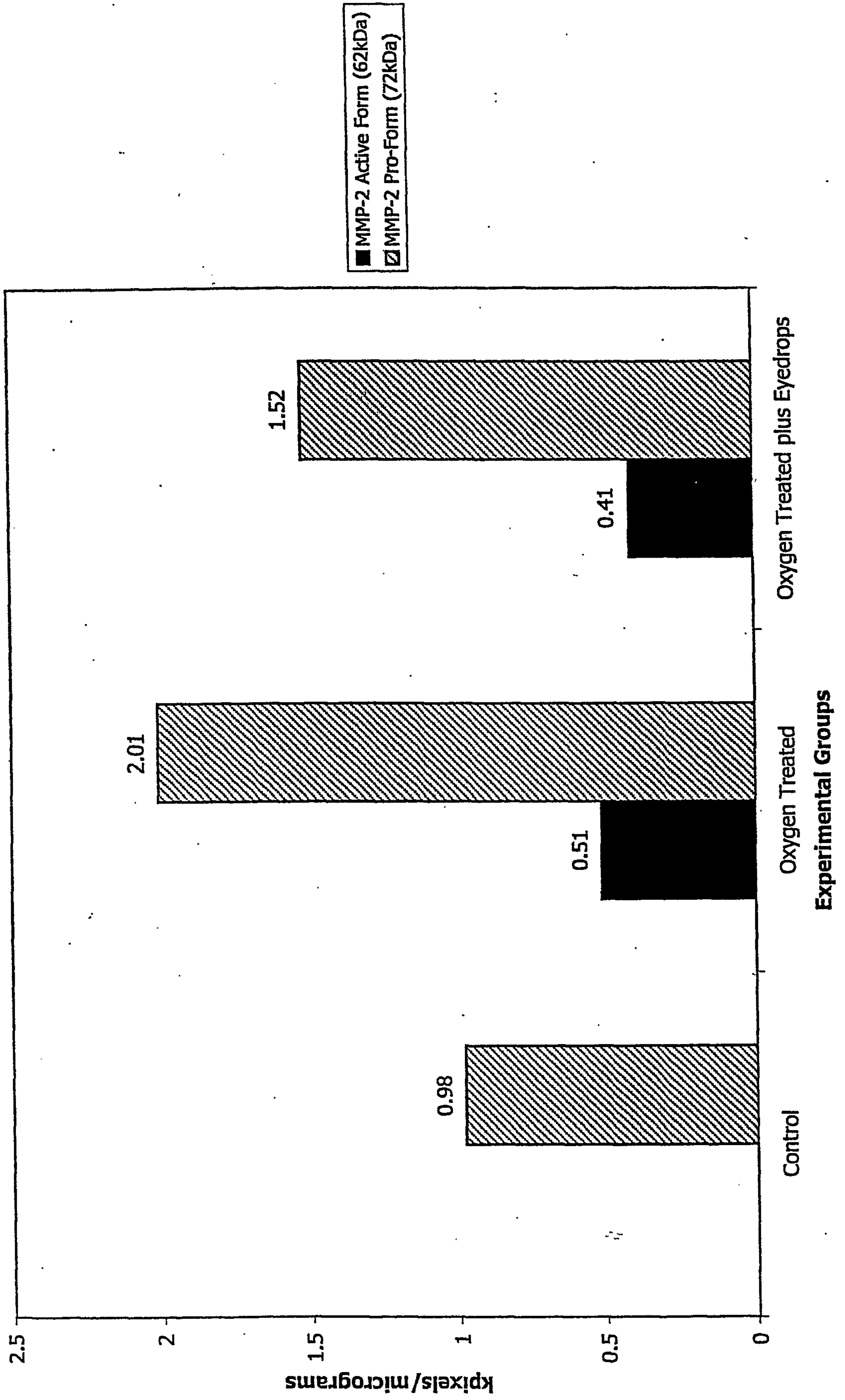


Figure 4

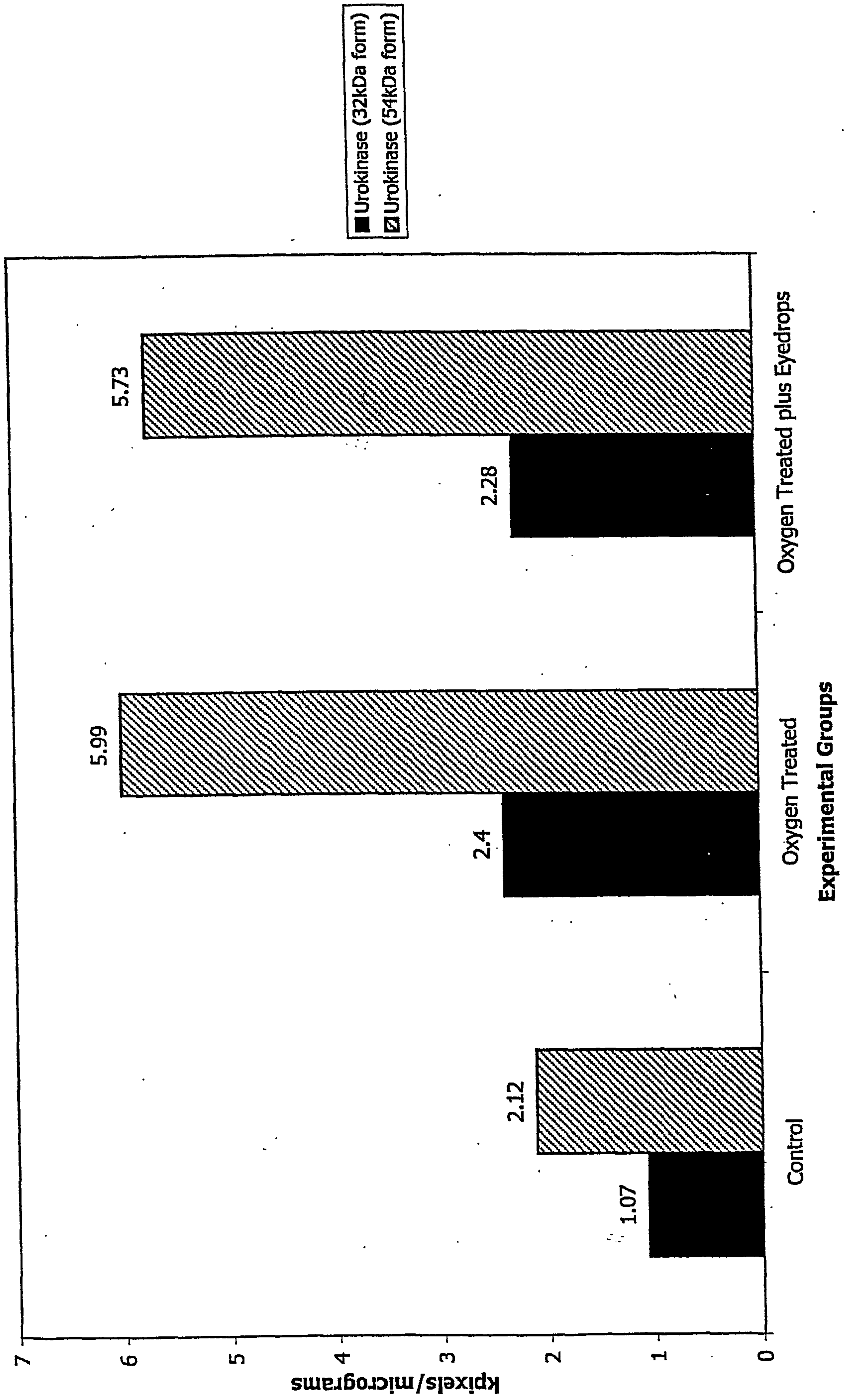


Figure 5

