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Methods and compositions for treatment of ocular neovascularization and neural injury
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ABSTRACT

Methods and compositions for protecting ocular neural tissue from damage. The invention includes combining electromagnetic treatment with administration of a neuroprotectant.

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**ORIGINAL
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Invention Title: Methods and compositions for treatment of ocular
neovascularization and neural injury

The following statement is a full description of this invention, including the best method of
performing it known to me:-

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METHODS AND COMPOSITIONS FOR TREATMENT OF OCULAR
NEOVASCULARIZATION AND NEURAL INJURY

This application is a divisional of Australian
Patent Application No. 2002230567, the entire disclosure
5 of which is incorporated herein by reference.

Background Of The Invention

Loss of visual acuity is a common problem
associated with aging and with various conditions of
10 the eye. Particularly troublesome is the development
of unwanted neovascularization in the cornea, retina
or choroid. Choroidal neovascularization leads to
hemorrhage and fibrosis, with resultant visual loss in
a number of recognized eye diseases, including macular
15 degeneration, ocular histoplasmosis syndrome, myopia,
diabetic retinopathy and inflammatory diseases.

Age-related macular degeneration (AMD) is the
leading cause of new blindness in the elderly, and
choroidal neovascularization is responsible for 80% of
20 the severe visual loss in patients with this disease.
Although the natural history of the disease is
eventual quiescence and regression of the
neovascularization process, this usually occurs at the
cost of sub-retinal fibrosis and vision loss.

25 Traditional treatment of AMD relies on occlusion
of the blood vessels using laser photocoagulation.
However, such treatment requires thermal destruction
of the neovascular tissue, and is accompanied by full-
thickness retinal damage, as well as damage to medium
30 and large choroidal vessels. Further, the subject is
left with an atrophic scar and visual scotoma.

Moreover, recurrences are common, and visual prognosis is poor.

Recently, forms of photocoagulation have been devised which attempt to reduce the damage attendant to traditional photocoagulation. For example, transpupillary thermotherapy (TTT) utilizes a low intensity laser in combination with a large "spot" (irradiation focal point) size and long exposure to close choroidal neovascularization and thereby treat macular degeneration. This procedure is said to reduce the amount of secondary damage seen in the use of traditional photocoagulation procedures.

Photodynamic Therapy

Recent research in the treatment of neovascularization have had the aim of causing more selective closure of the blood vessels, in order to preserve the overlying neurosensory retina. One such strategy is a treatment termed photodynamic therapy or PDT, which relies on low intensity light exposure of photosensitized tissues to produce lesions in the newly developing blood vessels. In PDT, photoactive compounds are administered and allowed to reach a particular undesired tissue which is then irradiated with a light absorbed by the photoactive compound. This results in destruction or impairment of the tissue immediately surrounding the locus of the photoactive compound without the more extensive ocular tissue damage seen when photocoagulation is used.

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Photodynamic therapy of conditions in the eye has been attempted over the past several decades using various photoactive compounds, e.g., porphyrin derivatives, such as hematoporphyrin derivative and

5 Photofrin porfimer sodium; "green porphyrins", such as benzoporphyrin derivative (BPD), MA; and phthalocyanines. Photodynamic treatment of eye conditions has been reported to actually enhance the visual acuity of certain subjects in some

10 circumstances. U.S. Patent No. 5,756,541.

However, although generally more safe than photocoagulation, there are certain dangers involved in performing PDT. For example, low intensity lasers in conjunction with the systemic injection of

15 vertporfin is currently the only approved PDT for treatment of age-related macular degeneration. But studies have shown that the use of vertporfin at high doses (12 and 18 mg/m²) result in long term or permanent scarring of the retina, chronic absence of photoreceptor cells, and optic nerve atrophy. Reinke et al., *Ophthalmology* 106:1915 (October 1999), incorporated by reference herein. At lower

20 concentrations of vertporfin (e.g., about 6 mg/m²) PDT is effective to slow vascular outgrowth and associated edema somewhat, but treatment appears to be necessary every few months.

Additionally, while PDT is clearly efficacious in some patients, this mode of treatment has resulted in a lower percentage of patients reporting an increase

30 in visual acuity, or a halting in the progression of visual deterioration, than would be expected

theoretically. The reasons for this have not been clearly understood in the literature, but may relate to PDT-induced neurosensory damage which limits efficacy.

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The Alpha Adrenergic Receptors

Human adrenergic receptors are integral membrane proteins which have been classified into two broad classes, the alpha and the beta adrenergic receptors. Both types mediate the action of the peripheral sympathetic nervous system upon binding of catecholamines, norepinephrine and epinephrine.

Norepinephrine is produced by adrenergic nerve endings, while epinephrine is produced by the adrenal medulla. The binding affinity of adrenergic receptors for these compounds forms one basis of the classification: alpha receptors tend to bind norepinephrine more strongly than epinephrine and much more strongly than the synthetic compound isoproterenol. The preferred binding affinity of these hormones is reversed for the beta receptors. In many tissues, the functional responses, such as smooth muscle contraction, induced by alpha receptor activation are opposed to responses induced by beta receptor binding.

Subsequently, the functional distinction between alpha and beta receptors was further highlighted and refined by the pharmacological characterization of these receptors from various animal and tissue sources. As a result, alpha and beta adrenergic

receptors were further subdivided into α_1 , α_2 , β_1 , and β_2 subtypes.

Functional differences between α_1 and α_2 receptors have been recognized, and compounds which exhibit selective binding between these two subtypes have been developed. Thus, in WO 92/0073, the selective ability of the R(+) enantiomer of terazosin to selectively bind to adrenergic receptors of the α_1 subtype was reported. The α_1/α_2 selectivity of this compound was disclosed as being significant because agonist stimulation of the α_2 receptors was said to inhibit secretion of epinephrine and norepinephrine, while antagonism of the α_2 receptor was said to increase secretion of these hormones. Thus, the use of non-selective alpha-adrenergic blockers, such as phenoxybenzamine and phentolamine, was said to be limited by their induction, through the α_2 adrenergic receptors, of increased concentrations of plasma catecholamine and attendant physiological sequelae (increased heart rate and smooth muscle contraction).

For a general background on the α -adrenergic receptors, the reader's attention is directed to Robert R. Ruffolo, Jr., α -Adrenoreceptors: Molecular Biology, Biochemistry and Pharmacology, (Progress in Basic and Clinical Pharmacology series, Karger, 1991), incorporated by reference herein, in which the basis of α_1/α_2 subclassification, the molecular biology, signal transduction, agonist structure-activity relationships, receptor functions, and therapeutic

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applications for compounds exhibiting α -adrenergic receptor affinity is explored.

The cloning, sequencing and expression of alpha receptor subtypes from animal tissues has led to the
5 subclassification of the α_1 adrenoreceptors into the further classifications of α_{1A} , α_{1B} , and α_{1D} . Similarly, the α_2 adrenoreceptors have also been classified α_{2A} , α_{2B} , and α_{2C} receptors. Each α_2 receptor subtype
10 appears to exhibit its own pharmacological and tissue specificities. Compounds having a degree of specificity for one or more of these subtypes may be more specific therapeutic agents for a given
indication than the currently employed α_2 receptor pan-agonists (such as the drugs clonidine and
15 brimonidine).

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A shows that brimonidine inhibits the
20 post PDT decrease in retinal functionality as compared to a saline control.

Figure 1B shows that brimonidine does not affect the area of ablation of CNV following PDT.

Figure 2B shows that Alphagan[®] (brimonidine) has
25 no effect on retinal thickness in non-PDT-treated rabbit eyes.

Figure 2B shows that brimonidine decreases the increase in retinal thickness (edema) appearing after
PDT treatment.

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SUMMARY OF THE INVENTION

Disclosed herein are compositions and methods of protecting ocular neural tissue from damage caused by electromagnetic irradiation of the retina comprising delivering to a patient's ocular neural tissue an amount of a neuroprotectant compound effective to protect a plurality of ocular neurons from cell death as compared to ocular neuron cell death following such irradiation observed in the absence of the administration of said neuroprotectant.

Also disclosed herein are compositions and methods for the treatment of ocular neovascularization, including the reduction of neurosensory function, which is attendant to current therapies such as photocoagulation and PDT. Further disclosed herein is an improved method of performing photodynamic therapy comprising treating the patient with an effective amount of a neuroprotective agent, selected from alpha adrenergic receptor modulators. Preferably, the alpha adrenergic receptor modulator is an alpha adrenergic receptor agonist. In a further preferred embodiment, the alpha receptor agonist is an alpha 2 receptor agonist, even more preferably an alpha 2B and/or an alpha 2C agonist. It is preferred that these agents be at least selective, and even specific, for the indicated receptors or receptor subtypes.

Still further disclosed herein is a method for reducing or eliminating a decrease in neurosensory retinal function following laser treatment of choroidal neovascularization (CNV) while maintaining the vascular occlusion therapeutic effect of such therapy, the method comprising the steps: a) administering to a mammal having a CNV a therapeutically effective amount of an alpha receptor

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agonist, b) subjecting said mammal to laser irradiation of the retinal locus of the CNV; wherein the amount of neurosensory retinal function following steps a) and b) is greater than when said mammal is subjected to step b) without step a). In a preferred embodiment, the mammal is given a therapeutically effective amount of a pharmaceutically acceptable photoactivated dye capable of accumulation in the locus of a choroidal neovascularization and destroying tissue when exposed to light of the same wavelength as the laser.

In a first aspect, the present invention provides a method of protecting ocular neural tissue of a patient's eye from damage caused by a photodynamic therapy (PDT) treatment, the method comprising the steps of:

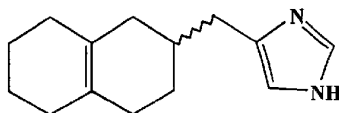
- a) administering a PDT treatment to the eye of the patient, and;
- b) delivering a composition to said patient's ocular neural tissue, wherein the composition comprises an amount of brimonidine effective to protect a plurality of ocular neurons from cell death caused by a photoactive component of the PDT treatment, as compared to ocular neuron cell death observed in a patient who has received PDT in the absence of the administration of said amount of brimonidine.

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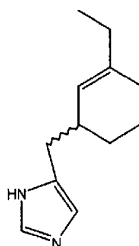
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In these methods, the alpha adrenergic receptor agonist is preferably an alpha 2 selective agonist, even more preferably an alpha 2B and/or alpha 2C selective agonist, most preferably, an alpha 2B selective agonist. In one preferred embodiment the alpha 2 selective agonist is selected from brimonidine and clonidine.

Other alpha 2B selective compounds include AGN 960, AGN 795 and AGN 923. The structure of AGN 960 is presented elsewhere in this patent application. The structure of AGN 795 is as follows:



The structure of AGN 923 is as follows:



By "effective amount" of a neuroprotective agent (such as an alpha adrenergic agonist) is meant an

amount effective to reduce the amount of cell death among the neurons of the retina and optic nerve (e.g., photoreceptors, retinal ganglion cells, and bipolar cells, or any of these) caused by the photoactive component of laser treatment as compared to a similarly situated CNV patient receiving laser treatment who does not receive treatment with the neuroprotective agent.

In another embodiment, the invention is drawn to an improved method of performing photodynamic or photocoagulation therapy comprising treating the patient with an effective amount of an agent effective to protect the neurons of the retina and optic nerve (e.g., photoreceptors) from damage caused by laser irradiation or the photoactive component of PDT treatment (neuroprotective agent).

An additional benefit of this therapy is the resultant reduction in edema and extravascularization of fluid that laser treatment causes.

By "effective amount" of a neuroprotective agent is meant an amount of such agent effective to reduce the extent to which, or the rate at which, new blood vessels are formed in the retina of a CNV patient as compared to a similarly situated CNV patient not given the neuroprotective agent.

In a third embodiment, the invention is directed to an improved method of performing photodynamic therapy comprising treating the patient with an effective amount of a neuroprotective agent, and irradiating the CNV with laser light sufficient to directly or indirectly cause destruction of the CNV.

In another preferred aspect, the invention is drawn to an improved method of performing photodynamic therapy comprising treating the patient with an amount of a neuroprotective agent protect neural cells so as to thereby increase the amount of time necessary between PDT treatments and to slow the progression of ARMD and other ocular conditions in which

neovascularization plays a part (for example ocular histoplasmosis syndrome (OHS) and pathogenic myopia) beyond that obtained by PDT or photocoagulation alone.

When an alpha adrenergic agonist or another agent having neuroprotective activity is used in conjunction with PDT or photocoagulation, it is preferred that the amount of such agent administered to the patient is an effective neuroprotective dose.

Determining the absolute dosage of the neuroprotective agent depends upon a number of factors, including the means of administration and delivery and the form of the drug. For intraocular delivery agent, such as by intravitreal or subretinal injection, dosages are preferably in the range of about 0.1 ug to about 100 ug per eye; more preferably in the range of about 0.20 ug to about 50 ug per eye; even more preferably in the range of about 0.5 ug to about 10 ug per eye.

The neuroprotective agent may be delivered by any means effective to expose the retinal and optic nerve cells to the agent. Thus, such agents may be delivered systemically, such as by intravenous, intramuscular, or subcutaneous injection, or by oral delivery. Alternatively, the neuroprotective and/or

neovascularization-inhibiting agent(s) may be delivered by direct injection into the eye, such as into the anterior chamber, posterior chamber or vitreous chamber, or by subretinal injection. The
5 reagent may also be delivered topically to the ocular surface.

Another delivery method provides for sustained delivery of the neuroprotective agent using an intraocular implant. Such implants may be, for
10 example, a biodegradable and/or biocompatible implant or insert such as the ocular implants and inserts disclosed in United States Patents No. 5,443,505, 5,824,072, 5,766,242; 4,853,224; 4,997,652; 5,164,188; 5,632,984; and 5,869,079, incorporated by reference
15 herein. Such implants may be inserted into a chamber of the eye, such as the anterior, posterior or anterior chambers, or may be implanted in the sclera, transchoroidal space, or an avascularized region exterior to the vitreous.

20

DETAILED DESCRIPTION OF THE INVENTION

The present invention is drawn to therapeutic
25 methods and compositions for the treatment of intraocular neovascularization associated with conditions such as age-related macular degeneration (ARMD), diabetic retinopathy, ocular histoplasmosis syndrome, and pathologic myopia.

30 The invention is more particularly concerned with therapeutic methods combining retinal photocoagulation

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or photodynamic therapy (PDT) with a neuroprotectant agent, preferably with an alpha adrenergic agonist.

In a preferred embodiment, the agent is an alpha 2 selective agonist; even more preferably an alpha 2B

5 and/or alpha 2C selective agonist. One can also combine the neuroprotective alpha adrenergic agonist with other neuroprotective agents to take advantage of different mechanistic means of providing neuroprotection.

10 In a preferred aspect of this embodiment of the invention, the neuroprotective agent is administered to the patient sufficiently prior to photocoagulation (such as TTT) or PDT treatment so as to be available to protect nerve cells upon the commencement of
15 therapy. In another aspect of the invention, the alpha adrenergic receptor agonist is administered a sufficient time following photocoagulation or PDT treatment to forestall nerve death due to such treatment.

20 Such methods are applicable to any photocoagulation method or to PDT treatment which makes use of any photoactive compound. Such photoactive compounds may include derivatives of hematoporphyrin, as described in U.S. Patents No. 25 5,028,621; 4,866,168; 4,649,151; and 5,438,071. pheophorbides are described in U.S. Pat. Nos. 5,198,460; 5,002,962; and 5,093,349; bacteriochlorins in U.S. Pat. Nos. 5,171,741 and 5,173,504; dimers and trimers of hematoporphyrins in U.S. Pat. Nos,
30 4,968,715 and 5,190,966. Other possible photoactive compounds include purpurins, merocyanines and

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porphycenes. All of the aforementioned patents are incorporated by reference herein. Of course, mixtures of photoactive compounds may be used in conjunction with each other.

- 5 A currently preferred photoactive compound is verteporfin (liposomal benzoporphyrin derivative). This compound is currently the only photoactive agent approved by the U.S. Food and Drug Administration for treatment of choroidal neovascularization in
- 10 conjunction with photodynamic therapy.

- The photoactive agent is formulated so as to provide an effective concentration to the target ocular tissue. The photoactive agent may be coupled to a specific binding ligand which may bind to a specific
- 15 surface component of the target ocular tissue, such as a cell surface receptor or, if desired, may be formulated with a carrier that delivers higher concentrations of the photoactive agent to the target tissue. Exemplary ligands may be receptor antagonists
- 20 or a variable region of an immunoglobulin molecule.

- The nature of the formulation will depend in part on the mode of administration and on the nature of the photoactive agent selected. Any pharmaceutically acceptable excipient, or combination thereof,
- 25 appropriate to and compatible with the particular photoactive compound may be used. Thus, the photoactive compound may be administered as an aqueous composition, as a transmucosal or transdermal composition, or in an oral formulation. The
- 30 formulation may also include liposomes. Liposomal compositions are particularly preferred especially

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where the photoactive agent is a green porphyrin.

Liposomal formulations are believed to deliver the green porphyrin with a measure of selectivity to the low-density lipoprotein component of plasma which, in

5 turn acts as a carrier to deliver the active ingredient more effectively to the desired site. Increased numbers of LDL receptors have been shown to be associated with neovascularization, and by increasing the partitioning of the green porphyrin
10 into the lipoprotein phase of the blood, it appears to be delivered more efficiently to neovasculature.

Consistent with the chosen formulation, the photoactive compound may be delivered in a variety of ways. For example, delivery may be oral, peritoneal,
15 rectal, or topical (e.g., by installation directly into the eye). Alternatively, delivery may be by intravenous, intramuscular or subcutaneous injection.

The dosage of the photoactive compound may vary, according to the activity of the specific compound(s)
20 chosen, the formulation, and whether the compound is joined to a carrier and thus targeted to a specific tissue as described above. When using green porphyrins, dosages are usually in the range of 0.1-50 mg/M² of body surface area; more preferably from about
25 1-10 mg/M² or from about 2-8 mg/M². Obviously, parameters to be considered when determining the dosage include the duration and wavelength of the light irradiation, the nature of the photochemical reaction induced by the light irradiation, and the
30 dye-to-laser time period.

Light irradiation is performed a sufficient time after the administration of the photoactive compound so as to permit the compound to reach its target tissue. Upon being irradiated with the wavelength(s) appropriate to the compound(s) chosen, the compound enters an excited state and is thought to interact with other compounds to form highly reactive intermediates which can then destroy the target endothelial tissue, causing platelet aggregation and thrombosis. Fluence of the irradiation may vary depending on factors such as the depth of tissue to be treated and the tissue type - generally it is between about 25 and about 200 Joules/cm². Irradiance typically is between about 150 and about 900 mW/cm², but can also vary somewhat from this range.

Typically, light treatment is given about 5 minutes following administration of the photoactive drug. In a preferred embodiment, the photoactive drug is administered intravenously.

The other component(s) of the methods and composition of the present invention are a neuroprotective alpha adrenergic agent. Exemplary neuroprotective agents are, without exception, alpha 2 adrenergic pan-agonists such as brimonidine and clonidine, and alpha 2B and or alpha 2C selective agonists such as, without limitation, those mentioned in US Patent No. 6,313,172 and patent publications WO0178703, WO0178702, WO0100586 and WO9928300. These patents and patent applications are owned by the assignee of the present patent application, and are hereby incorporated by reference herein.

In a preferred aspect of the invention a neuroprotective agent comprising an alpha adrenergic agonist is administered to the eye to protect it during and after PDT treatment. In an even more

5 preferred embodiment of the invention, the neuroprotective agent is an alpha 2 selective agonist.

In a most preferred embodiment of the invention, the compound is an alpha 2B selective agonist.

Brimonidine has been reported to have
10 neuroprotective activity. Hence, US Patent No. 5,856,329 and Yoles E., et al., *Invest. Ophthalmol. Vis. Sci.* 40: 65 (1999) disclose this property of brimonidine; however, neither of these references makes any suggestion that brimonidine be used in the
15 treatment of CNV.

The neuroprotective alpha adrenergic agent(s) of the present invention are delivered in any manner in which it is effective to protect neurons and/or inhibit neovascularization incident to
20 photocoagulation or PDT treatment. Generally, the agent(s) is administered prior to laser treatment, so as to permit it to reach the ocular neural tissue before phototherapy. This will permit the agent(s) to have an immediate protective effect on neural cells.
25 However, the neovascularization-inhibiting benefits of such an agent can be realized even when given simultaneously with, or shortly after PDT treatment.

Additionally, the alpha adrenergic agents useful
30 in the present method may be joined, in a manner

similar to that of the photoactive compounds, to cell surface targeting ligands, such as portions of an antibody or immunologically active fragments to aid in targeting the drug to ocular cells, such as the optic nerve neurons and photoreceptors.

The neuroprotective alpha agonist agent may be formulated for oral delivery in, for example, a capsule, tablet or liquid, or for intravenous, intramuscular, or subcutaneous injection. In such a formulation, any suitable excipient may be added to such a formulation to stabilize the active ingredient and, particularly in the case of intravenous administration, to provide the necessary electrolyte balance. The alpha adrenergic agonists used in the methods of the present invention may also be formulated as a suppository or otherwise administered rectally. Formulations appropriate for rectal drug administration are well-known to those of skill in the art.

In yet another embodiment the alpha adrenergic agonist agents may be formulated within liposomes. The liposomes are then able to fuse with a cell membrane, thus delivering the nucleic acid to receptors located at the cell surface and within the cell.

As indicated above, the neuroprotective agents to be used in the present invention may be administered by systemic delivery, as by intravenous, intramuscular or subcutaneous injection. In addition, these agents may be delivered directly to the eye by biocompatible and/or biodegradable implants or inserts (such as

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those described in patents cited and incorporated by
reference above) containing the drug , or by direct
injection into the eye, for example by intravitreal
and/or subretinal injection. Alternatively, the alpha
5 adrenergic agents may be topically applied to the
surface in an drop.

The therapeutically effective dosage of such
agents will depend upon factors including the mode of
delivery, the specific activity of the polypeptide,
10 and the formulation in which the agent is fabricated.
Once a formulation and route of administration is
decided upon, determining a therapeutically effective
dose is routine in the pharmaceutical arts, and can be
readily determined without undue experimentation using
15 suitable animal models such as, without limitation,
non-human primates and rabbits.

Preferably, the dosage regimen of the
neuroprotective agent will be such to permit the
active agent to remain in contact with retinal cells
20 throughout the treatment period. Thus, the agent may
be administered, for example, once or twice a day for
12 weeks.

Example 1

25

A 74 year old patient presents with "wet" age-
related macular degeneration (ARMD) in the foveal
region of the right eye, and his condition is found to
be suitable for photodynamic therapy (PDT). For one
30 week prior to the date of scheduled treatment, the

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patient is given a topical dosage of brimonidine twice a day in a standard formulation.

The day of scheduled PDT treatment, the patient is administered 6 mg/M² of verteporfin. Fifteen
5 minutes after the start of the infusion, the patient is administered Irradiance of 600 mW/cm² and total fluence of 50 Joules/cm² from an Argon light laser.

Brimonidine administration is continued every two days throughout the 12 week evaluation period.

10 Evaluation of neural health is assayed 1 week, 4 weeks, and 12 weeks following treatment by visual inspection of the retina and test of visual acuity. The affected areas of the retina appear healthy with no whitening (indicating lack of discernable retina
15 damage) or edema one week following PDT treatment; this trend continues throughout the monitoring period.

Fluorescein angiography at same time points shows minimal leakage in the treated tissue after one week, and this minimal leakage continues throughout the
20 monitoring period. No evidence of renewed neovascularization can be seen 12 weeks following PDT treatment. Additionally, no evidence of optic nerve axon loss can be seen. Tests of visual acuity 4 and 12 weeks following combined PDT and PEDF treatment
25 show no discernable loss of vision, as a result of the treatment.

Example 2

30 Same facts as in Example 1, except that rather than being given topical brimonidine, the affected eye

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is given an biodegradable intraocular implant, by injection into the vitreous humor. The implant placed in the eye by intravitreal injection three days prior to PDT treatment ; and is readministered 10 days following PDT treatment. The retina is examined following the 12 week evaluation period.

Evaluation of neural health is assayed 1 week, 4 weeks, and 12 weeks following treatment by visual inspection of the retina and test of visual acuity.

The affected areas of the retina appear healthy with no whitening (indicating lack of discernable retina damage) one week following PDT treatment; this trend continues throughout the monitoring period. Additionally, no evidence of optic nerve axon loss can be seen. Tests of visual acuity 4 and 12 weeks following combined PDT and PEDF treatment show no discernable loss of vision as a result of the treatment.

Example 3

Brown Norway rats weighing 200-400 grams were treated intraperitoneally (i.p.) with either brimonidine, AGN 199960, or the saline vehicle. One hour later, the rats were unilaterally treated with PDT and evaluated by electroretinography 3-4 hours later. There were 4 rats in each treatment group.

PDT was conducted as follows: Mydriasis was induced in one eye of each rat with a drop of 0.5% tropicamide. Rats were then anesthetized with isoflurane and placed on a platform in front of a slit

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lamp coupled to a Coherent diode laser for verteporfin PDT (689 nm). Verteporfin was injected intravenously at a dose of 6 mg/m². One minute later, the retina of one eye was irradiated with a 3 mm size spot at 50 J/cm², 600 mW/cm² in the superior hemisphere above the optic disk. Three to four hours later, the treated animals were again dilated and anesthetized, then electroretinograms (ERGs) were evaluated in each eye.

ERGs are collected non-invasively by measuring mass-cell response arising due to retinal activity proceeding from a light stimulus. The first cells stimulated by a flash light stimulation are the photoreceptors at the outer retinal layer. This response is measured as an a-wave. As the signal is transduced to inner retinal neurons, a b-wave is produced. The a-wave reflects activity in the photoreceptors and the b-wave reflects activity in both photoreceptors and bipolar cells.

Before being subjected to the ERG test, the rats were placed in the dark (dark-adapted) for 15 minutes.

Two types of ERG apparatus were used to generate the results below. In the initial brimonidine experiment, each eye was evaluated separately. A Grass photostimulator was placed 10 cm from the recording eye and flashed a single white flash lasting 10 microseconds. A gold corneal ring electrode with a reference electrode attached to the lower eyelid detected retinal responses. For the AGN 199960 experiments, a Ganzfeld dome was used to generate a single flash and sensitive bipolar corneal electrodes were placed on both eyes, thus allowing simultaneous

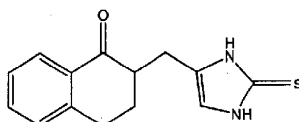
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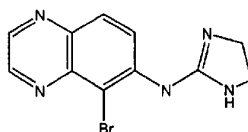
ERGs to be done. A cushioning agent on the cornea (methylcellulose) was used in each case, and the responses were amplified and stored in a computer. The results reported are a-wave amplitudes, which

- 5 appear to be the ERG parameter most affected in clinical PDT. As can be seen below, the loss in retinal function induced by PDT was inhibited by an alpha-2 receptor pan agonist (brimonidine) and a selective alpha-2B receptor agonist (AGN 960).

- 10 AGN 960 has the following structure:



Brimonidine has the following structure:



15

Agent	Dose	N	A Wave Amplitude (uV)		% Control
			PDT Eye	Control	
				Eye	
Vehicle	1 ml/kg	4	70 ± 18	104 ± 17	67 ± 12
Brimonidine	1000 ug/kg	4	90 ± 15	91 ± 21	103 ± 8 *
Vehicle	1 ml/kg	4	120 ± 12	228 ± 17	53 ± 3
AGN 960	300	4	212 ± 16	218 ± 29	101 ± 13

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Table 1. A-wave reflects photoreceptor function. Animals were treated with the indicated agent or vehicle i.p. 1 hour prior to PDT. * = $p \leq 0.05$, comparison between drug and vehicle-treated animals utilizing an unpaired Student's t-test

Example 4

Seven pigmented rabbits were dosed with either 0.5 mls of 0.2% brimonidine (alphagan) or saline administered retrobulbarly in 1 eye of each rabbit. One hour later, the animals were treated with a 10 minute intravenous infusion of 0.2 mg/kg verteporfin, then the same eye was irradiated 10 minutes later in the lower fundus with a 689 nm diode laser at 50 J/cm², 600 mW/cm² and a spot size of 1.5 mm.

Treated eyes were then imaged by ocular coherence tomography; this method gives a measure of retinal thickness at the following time points after PDT (hours): 4, 24, 48, 72. Data are presented in Figure 1A and 1B; and show that brimonidine reduced the increase in retinal thickness (subretinal cyst + retina) in the lesion produced by PDT.

These examples illustrate certain embodiments of the present invention; however, it will be understood that the invention is solely defined by the claims that conclude this specification.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

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The claims defining the invention are as follows:

- 1) A method of protecting ocular neural tissue of a patient's eye from damage caused by a photodynamic therapy (PDT) treatment, the method comprising the steps of:
 - 5 a) administering a PDT treatment to the eye of the patient, and;
 - b) delivering a composition to said patient's ocular neural tissue, wherein the composition comprises an amount of brimonidine effective to protect a plurality of ocular
10 neurons from cell death caused by a photoactive component of the PDT treatment, as compared to ocular neuron cell death observed in a patient who has received PDT in the absence of the administration of said amount of brimonidine.
- 2) The method of claim 1 wherein said brimonidine is
15 administered at a time sufficiently before said PDT treatment to permit localisation within ocular tissue prior to said treatment.
- 3) The method of claim 1 wherein said brimonidine is administered intravenously.
- 20 4) The method of claim 1 wherein said brimonidine is administered through intraocular injection.
- 5) The method of claim 1 wherein said brimonidine is administered by subretinal injection.
- 6) The method of claim 1 wherein said brimonidine is
25 administered by intravitreal injection.
- 7) The method of any of the preceding claims 1 to 6 wherein said composition also comprises a therapeutically effective amount of an antiangiogenic compound.

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8) The method of claim 1 wherein said PDT treatment occurs prior to the administration of brimonidine to said ocular neural tissue.

9. The method of claim 1 wherein said PDT treatment
5 occurs following the administration of brimonidine to said ocular neural tissue.

10. A method of protecting ocular neural tissue of a patient's eye from damage caused by a photodynamic therapy treatment (PDT) said method being substantially as
10 hereinbefore described with reference to the Examples.

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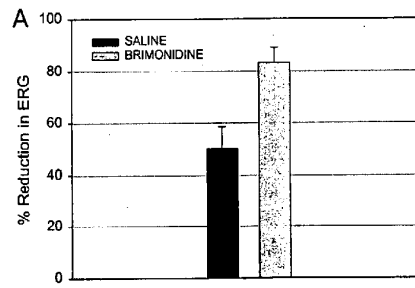


Fig. 1A

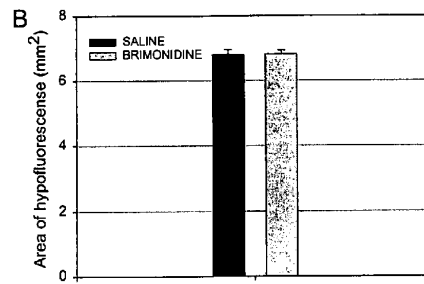


Fig. 1B

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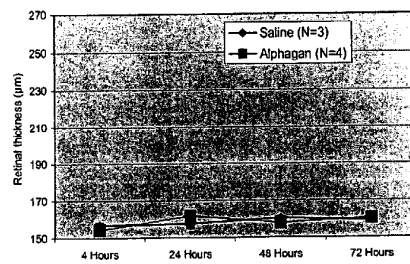


Fig. 2A

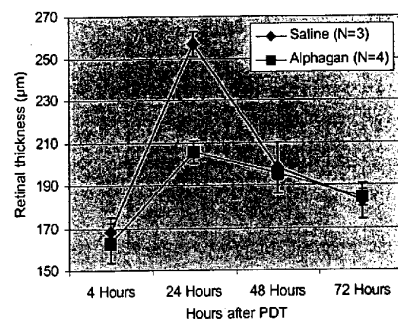


Fig. 2B