Further, there remains need for non-invasive method for inhibiting loss of retinal ganglion cells in a subject in need thereof. Various ocular diseases and disorders are characterized by death of retinal ganglion cells (RGCs). Accordingly, there remains a need for a non-invasive method for inhibiting loss of retinal ganglion cells (RGCs) in subjects that are suffering from an ocular disease, an ocular disorder or an ocular injury or are at risk of developing an ocular disease, an ocular disorder, or an ocular injury characterized and/or mediates by degeneration or death of retinal ganglion cells (RGCs).

SUMMARY OF THE ~~INVENTION~~DISCLOSURE

The present ~~invention~~disclosure is directed to non-invasive methods of treating ocular diseases, disorders and injuries that are associated with degeneration or death of retinal ganglion cells (RGCs) and to compositions useful in the methods. The methods of the ~~invention~~disclosure comprise topically administering to the surface of the eye of a subject a therapeutic oligonucleotide composition useful in promoting survival of retinal ganglion cells in a subject. Hitherto, oligonucleotides have been delivered to retinal ocular tissue by systemic delivery or intravitreal injection, methods associated with detrimental side effects and poor patient compliance, respectively. The present ~~invention~~disclosure provides topical ophthalmic compositions comprising an oligonucleotide, and non-invasive methods of use thereof for down regulating expression of a target gene associated with loss of the retinal ganglion cell in the retina of a subject, for rescuing retinal ganglion cells from apoptosis and for treating eye disorders.

Accordingly, in one aspect the present ~~invention~~disclosure provides a method of non-invasive delivery of an oligonucleotide to a retinal tissue in a subject suffering from an eye disorder, disease or injury comprising topically applying an ophthalmic composition comprising the oligonucleotide to the surface of the eye of the subject.

In another aspect the present ~~invention~~disclosure provides a method of non-invasive delivery of an oligonucleotide to a retinal ganglion cell in a subject suffering from an eye disorder comprising topically applying an ophthalmic composition comprising the oligonucleotide to the surface of the eye of the subject.

In yet another aspect, the present ~~invention~~disclosure provides a method of attenuating expression of a target gene associated with loss of a retinal ganglion cell in the retina in a subject suffering from an ocular disease, disorder or injury, which comprises topically (non-invasively) administering to the surface of the eye of the subject a pharmaceutical

composition comprising at least one oligonucleotide directed to the target mRNA product of the target gene, in an amount and over a period of time effective to attenuate expression of the gene in the retina of the subject.

In a further aspect, the present ~~invention~~disclosure provides a method of treating a subject suffering from retinal ganglion cell loss or retinal ganglion cell damage and providing ocular neuroprotection to a subject suffering from or at risk of developing an eye disease, disorder or injury. The method comprises topically administering to the surface of the eye of the subject an ophthalmic pharmaceutical composition comprising at least one oligonucleotide directed to a target gene in the retina of the subject, in an amount and over a period of time effective to inhibit retinal ganglion cell loss or retinal ganglion cell damage in the subject.

In various embodiments the ophthalmic pharmaceutical composition is formulated as a cream, a foam, a paste, an ointment, an emulsion, a liquid solution including an eye drop, a gel, spray, a suspension, a microemulsion, microspheres, microcapsules, nanospheres, nanoparticles, lipid vesicles, liposomes, polymeric vesicles, a patch, or a contact lens. In some embodiments the pharmaceutical composition is formulated as an eye drop. In preferred embodiments the ophthalmic composition is administered to the eye, for example, by instillation of an eye drop or by administration of a mist.

In certain embodiments the at least one target ocular mRNA is selected from an mRNA polynucleotide set forth in any one of SEQ ID NOS:1-58. In certain embodiments the at least one target gene is selected from a gene transcribed into an mRNA polynucleotide set forth in any one of SEQ ID NOS:1-58.

In some embodiments the at least one oligonucleotide is selected from chemically modified siRNA, unmodified siRNA, antisense, ribozyme, miRNA and shRNA. In preferred embodiments the at least one oligonucleotide is a chemically modified siRNA. In some embodiments the siRNA sense and antisense oligonucleotides are selected from sense and corresponding antisense oligonucleotide pairs shown in Tables B1-B36, set forth in SEQ ID NOS:59-33,596.

In some embodiments the eye disorder, disease or injury is selected from glaucoma, dry eye, diabetic retinopathy (DR), diabetic macular edema (DME) or age related macular degeneration (AMD). In other embodiments the ocular disorder, disease or injury is optic neuritis, central retinal vein occlusion, brunch retinal vein occlusion (BRVO). In further

embodiments the eye disorder, disease or injury is retinitis pigmentosa (RP), ischemic optic neuropathy or optic nerve injury. In further embodiments ocular disorder, disease or injury is retinopathy of prematurity (ROP) retinal ganglion degeneration, macular degeneration, hereditary optic neuropathy, metabolic optic neuropathy, optic neuropathy due to a toxic agent or neuropathy caused by adverse drug reactions or vitamin deficiency. In yet another embodiment the disorder is vision loss associated with a tumor.

In various embodiments the at least one siRNA compound is delivered to the eye of a subject as a liquid solution, including an eye drop. In various embodiments the present ~~invention~~disclosure provides a method for attenuating expression of a target ocular gene associated with loss of a retinal ganglion cell in a subject suffering from an ocular disease, disorder or injury, comprising topically applying to the surface of the eye of the subject an ophthalmic pharmaceutical composition formulated as an eye drop.

In various embodiments expression of a target ocular mRNA is attenuated in an ocular cells in the retina of a subject suffering from an eye disease, disorder, or injury. In various embodiments the ocular cell includes but is not limited to an acinar cell of the lacrimal gland, a ductal cell of the lacrimal gland, a retinal ganglion cell (RGC), a retinal pigment epithelial (RPE) cell, a choroidal cell, a corneal cell, a cell of the ciliary process or a cell of the trabecular meshwork or a combination thereof.

The present ~~invention~~disclosure provides a method for inhibiting loss of a retinal ganglion cell in a subject, comprising non-invasively administering to the surface of the eye of the subject an ophthalmic composition comprising a therapeutically effective amount of at least one siRNA which down regulates expression of a target gene associated with loss of the retinal ganglion cell in the retina of the subject, thereby inhibiting loss of a retinal ganglion cell. In certain embodiments two or more target genes are down regulated by the method according to the invention. In certain embodiments attenuating expression of at least one target gene (ocular mRNA) associated with loss of the retinal ganglion cell in the retina of the subject confers upon the eye neuroprotective properties. In various embodiments the at least one ocular target gene is selected from the list in Tables A1 to A4, set forth in SEQ ID NO:1-58.

In one embodiment the eye disorder is glaucoma. Thus the present ~~invention~~disclosure provides a method of inhibiting loss of a retinal ganglion cell in a subject suffering from glaucoma comprising topically (non-invasively) applying to the surface of the eye of the subject an ophthalmic composition comprising a therapeutically effective amount of at least one

siRNA which down regulates a target gene (target ocular mRNA) associated with loss of the retinal ganglion cell in the retina of the subject, thereby inhibiting loss of a retinal ganglion cell in the subject's eye. In preferred embodiments the siRNA is chemically modified. In some embodiments the chemically modified siRNA attenuates expression of gene (target ocular mRNA) in the retina of the subject's eye. In other embodiments the chemically modified siRNA attenuates expression of target ocular mRNA in the optic nerve of the subject's eye. In certain embodiments attenuating expression of at least one target gene (ocular mRNA) associated with loss of the retinal ganglion cell in the retina of the subject is effective to treat glaucoma. In certain embodiments the at least one target gene is selected from the list in Table A1 set forth in SEQ ID NO:1-35. In certain preferred embodiments the target gene is selected from CASP2 (SEQ ID NO:1-2), ASPP1 (SEQ ID NO:4), TP53BP2 (SEQ ID NO:6-7), BNIP3 (SEQ ID NO:12), RTP801L (SEQ ID NO:14), ACHE (SEQ ID NO:19-20), ADRB1 (SEQ ID NO:21) and CAPNS1 (SEQ ID NO:28-29). In various embodiments the gene is set forth in SEQ ID NOS:1-2. In some embodiments the siRNA sense and antisense strands are selected from pairs of oligonucleotide sequences set forth in SEQ ID NOS:8515-9516.

In another embodiment the eye disorder is dry-eye. Thus the present ~~invention~~disclosure provides a method of inhibiting loss of a retinal ganglion cell in a subject suffering from dry-eye. The method comprises topically (non-invasively) administering to the surface of the eye of the subject an ophthalmic composition comprising a therapeutically effective amount of at least one siRNA which down regulates a target gene (target ocular mRNA) associated with loss of the retinal ganglion cell in the retina of the subject, thereby inhibiting loss of a retinal ganglion cell in the subject's eye. In preferred embodiments the siRNA is chemically modified. In certain embodiments attenuating expression of at least one target ocular mRNA is effective to treat dry-eye disorder. In certain embodiments attenuating expression of at least one target gene associated with loss of retinal ganglion cells is effective to reduce the symptoms of dry-eye. In certain embodiments the at least one target gene (ocular target mRNA) is expressed in retinal ganglion cell in the eye of the subject. In certain embodiments the at least one target gene (ocular target mRNA) is expressed in the lacrimal gland in the eye of the subject. In certain embodiments the at least one target gene is selected from Table A2 set forth in any one of SEQ ID NO: 5 (p53), SEQ ID NO:8 – 10 (LRDD), SEQ ID NO:26 – 27 (SHC1) and SEQ ID NO:30 – 44 (FAS and FAS ligand). In some embodiments the target gene is selected from FAS, FAS

ligand (FASL), p53, LRDD, PARP1, AIF (apoptosis inducing factor), NOS1, NOS2A, XIAP and SHC1-SHC. In certain preferred embodiments the target gene is set forth in any one of SEQ ID NO:36 - SEQ ID NO: 43 or SEQ ID NO:44. In some embodiments the siRNA sense and antisense strands are selected from pairs of oligonucleotide sequences set forth in SEQ ID NOS: 13,225-15,224.

In another embodiment the eye disorder is AMD, DR or DME. Thus, the present ~~invention~~disclosure provides a method of inhibiting loss of a retinal ganglion cell in a subject suffering from AMD, DR or DME. The method comprises topically (non-invasively) administering to the surface of the eye of the subject an ophthalmic composition comprising a therapeutically effective amount of at least one siRNA which down regulates a target gene (target ocular mRNA) associated with loss of the retinal ganglion cell in the retina of the subject, thereby inhibiting loss of a retinal ganglion cell in the subject's eye. In preferred embodiments the siRNA is chemically modified. In certain embodiments attenuating expression of at least one target gene associated with loss of retinal ganglion cells is effective to treat AMD, DR or DME. In certain embodiments attenuating expression of at least one target gene associated with loss of retinal ganglion cells is effective to reduce the symptoms of AMD, DR or DME. In certain embodiments the administration of at least one siRNA attenuates expression of at least one target gene (ocular mRNA) in a retinal ganglion cell in the subject's eye. In certain embodiments the administration of at least one siRNA attenuates expression of at least one target gene (target ocular mRNA) in the choroid in the subject's eye. In certain embodiments the at least one target gene is listed in Table A3 set forth in any one of SEQ ID NOS:1-2, 3, 5, 6-7, 8-10, 12, 13, 24-25, 26-27, 30-35, 45-53. In certain preferred embodiments the siRNA targets CTSD, RTP801 and BNIP3. In certain preferred embodiments the disorder is DR and the siRNA targets mRNA set forth in SEQ ID NOS:48-53. In some embodiments the siRNA sense and antisense strands are selected from any one of sequences set forth in SEQ ID NOS:24575-29594. In certain preferred embodiments the disorder is AMD and the siRNA targets gene set forth in SEQ ID NO:3 and the siRNA sense and antisense strands are selected from any one of sequences set forth in SEQ ID NOS:11285-12224. In some embodiments the siRNA sense and antisense strands are selected from pairs of oligonucleotide sequences set forth in SEQ ID NOS:24575-29594.

In a further embodiment the eye disorder is Retinitis pigmentosa (RP). Thus, the present ~~invention~~disclosure provides a method of inhibiting loss of a retinal ganglion cell in a subject

suffering from RP. The method comprises topically (non-invasively) administering to the surface of the eye of the subject an ophthalmic composition comprising a therapeutically effective amount of at least one siRNA which down regulates a target gene (target ocular mRNA) associated with loss of the retinal ganglion cell in the retina of the subject, thereby inhibiting loss of a retinal ganglion cell in the subject's eye. In preferred embodiments the siRNA is chemically modified. In certain embodiments attenuating expression of at least one target gene associated with loss of retinal ganglion cells is effective to RP. In certain embodiments attenuating expression of at least one target gene associated with loss of retinal ganglion cells is effective to reduce the symptoms of RP. In certain embodiments the at least one target ocular mRNA is product of a gene selected from a gene listed in Table A4 which is transcribed into mRNA set forth in any one of SEQ ID NOS: 3, 14, 26-35, 54-57. In some embodiments the target ocular mRNA is product of a gene selected from the group consisting of CASP1, CASP3, CASP12, RTP801, RTP801L, CAPNS1, PARP1, AIF, NOS1, NOS2, XIAP and SHC1-SHC. In certain preferred embodiments the siRNA targets mRNA set forth in SEQ ID NOS:56-57.

In another aspect the ~~invention~~disclosure features a method of rescuing a retinal ganglion cell from apoptosis in a subject, comprising non-invasively applying to the surface of the eye of the subject an ophthalmic composition comprising a therapeutically effective amount of at least one siRNA to a target gene in the retina of the subject, thereby rescuing retinal ganglion cell from apoptosis in the subject. In preferred embodiments the at least one siRNA is a chemically modified. In some embodiments the target gene is set forth in any one of SEQ ID NO:1- 58. In various embodiments the siRNA sense and antisense oligonucleotides are selected from sense and corresponding antisense oligonucleotides shown in tables B1-B36 and set forth in SEQ ID NOS:59-33,596.

In another aspect, the ~~invention~~disclosure provides method for promoting survival of a retinal ganglion cell in a subject displaying signs or symptoms of an ocular neuropathy, comprising non-invasively administering to the surface of the eye of the subject an ophthalmic composition comprising a therapeutically effective amount of at least one siRNA to a target gene in the retina of the subject, thereby promoting survival of a retinal ganglion cell in the subject. In preferred embodiments the at least one siRNA is a chemically modified. In certain embodiments the signs or symptoms of an ocular neuropathy are mediated by apoptosis. In some embodiments the target gene is set forth in any one of SEQ ID NO:1- 58. In various embodiments the siRNA sense and antisense

oligonucleotides are selected from sense and corresponding antisense oligonucleotides set forth in SEQ ID NOS:59-33,596.

In yet another aspect, the ~~invention~~disclosure is directed to a method for preventing, treating or alleviating the effects of an ocular disease associated with death of a retinal ganglion cell in a subject, comprising non-invasively applying to the surface of the eye of the subject an ophthalmic composition comprising a therapeutically effective amount of at least one siRNA to a target gene in the retina of the subject, thereby preventing, treating or alleviating the effects of an ocular disease associated with death of a retinal ganglion cell in the subject. In preferred embodiments the at least one siRNA is a chemically modified. In some embodiments the target gene is set forth in any one of SEQ ID NO:1- 58. In various embodiments the siRNA sense and antisense oligonucleotides are selected from sense and corresponding antisense oligonucleotide pairs shown in Tales B1-B36, set forth in SEQ ID NOS:59-33,596.

Another aspect of the ~~invention~~disclosure provides for a method for treating or preventing retinal ganglion cell death in a subject, comprising non-invasively applying to the surface of the eye of the subject an ophthalmic pharmaceutical composition which comprises: (a) a therapeutically effective amount of at least one siRNA to a target gene in the retina of the subject, and (b) a pharmaceutically acceptable excipient or carrier or mixture thereof, and thereby treating or preventing retinal ganglion cell death in the subject. In preferred embodiments the at least one siRNA is a chemically modified. In some embodiments the target gene is set forth in any one of SEQ ID NO:1- 58. In various embodiments the siRNA sense and antisense oligonucleotides are selected from sense and corresponding antisense oligonucleotides set forth in SEQ ID NOS:59-33,596.

In another aspect, the present ~~invention~~disclosure is directed to a method preventing retinal ganglion cell death mediated by elevated intraocular pressure (IOP) in the eye of a subject, comprising non-invasively administering to the surface of the eye of the subject an ophthalmic composition comprising a therapeutically effective amount of at least one siRNA to a target gene in the retina of the subject, thereby preventing retinal ganglion cell death in the subject. In preferred embodiments the at least one siRNA is a chemically modified. In a particular embodiment according to this method the subject is afflicted with glaucoma. In some embodiments the target gene is set forth in any one of SEQ ID NO:1- 58. In various embodiments the siRNA sense and antisense oligonucleotides are

selected from sense and corresponding antisense oligonucleotides set forth in SEQ ID NOS:59-33,596.

The present ~~invention~~disclosure further provides a method of delaying, preventing or rescuing a retinal cell from death in a subject suffering from elevated IOP comprising non-invasively applying to the surface of the eye of the subject an ophthalmic composition comprising a therapeutically effective amount of at least one siRNA to a target gene associated with death of the RGC in the retina of the subject, thereby delaying, preventing or rescuing the retinal cell from injury or death and wherein intraocular pressure (IOP) remains substantially elevated. In preferred embodiments the at least one siRNA is a chemically modified. In a particular embodiment according to this method the subject is afflicted with glaucoma. In some embodiments the target gene is set forth in any one of SEQ ID NO:1- 58. In various embodiments the siRNA sense and antisense oligonucleotides are selected from sense and corresponding antisense oligonucleotides set forth in SEQ ID NOS:59-33,596.

The present ~~invention~~disclosure further provides a method of treating a subject suffering from retinal ganglion cell loss or retinal ganglion cell damage, comprising non-invasively administering to the surface of the eye of the subject an ophthalmic composition comprising a therapeutically effective amount of at least one siRNA to a target gene in the retina of the subject, thereby treating the subject or reducing retinal ganglion cell death in the subject. In preferred embodiments the at least one siRNA is a chemically modified. In some embodiments the target gene is set forth in any one of SEQ ID NO:1- 58. In various embodiments the siRNA sense and antisense oligonucleotides are selected from sense and corresponding antisense oligonucleotides set forth in SEQ ID NOS:59-33,596.

The present ~~invention~~disclosure further provides a method for lowering retinal ganglion cell loss and providing ocular neuroprotection to a subject in need thereof, comprising non-invasively applying to the surface of the eye of the subject an ophthalmic composition comprising a therapeutically effective amount of at least one siRNA to a target gene in the retina of the subject, thereby lowering retinal ganglion cell loss and providing ocular neuroprotection to the subject. In preferred embodiments the at least one siRNA is a chemically modified. In some embodiments the target gene is set forth in any one of SEQ ID NO:1- 58. In various embodiments the siRNA sense and antisense oligonucleotides are selected from sense and corresponding antisense oligonucleotide pairs shown in Tables B1-B36, set forth in SEQ ID NOS:59-33,596.

The present ~~invention~~disclosure further provides a method for preventing visual field loss associated with loss of retinal ganglion cells in a subject, comprising non-invasively administering to the surface of the eye of the subject an ophthalmic composition comprising a therapeutically effective amount of at least one siRNA to a target gene in the retina of the subject, thereby preventing visual field loss in the subject. In preferred embodiments the at least one siRNA is a chemically modified. In some embodiments the target gene is set forth in any one of SEQ ID NO:1- 58. In various embodiments the siRNA sense and antisense oligonucleotides are selected from sense and corresponding antisense oligonucleotide pairs shown in Tables B1-B36, set forth in SEQ ID NOS:59-33,596.

In another aspect, the present ~~invention~~disclosure provides an ophthalmic composition for non-invasive treatment of an ocular disease associated with loss of a retinal ganglion cell in a subject, comprising: (a) a therapeutically effective amount of at least one siRNA to a target gene in the retina of the subject, and (b) a pharmaceutically acceptable excipient or carrier or mixture thereof. In preferred embodiments the at least one siRNA is a chemically modified. In some embodiments the target gene is set forth in any one of SEQ ID NO:1- 58. In various embodiments the siRNA sense and antisense oligonucleotides are selected from sense and corresponding antisense oligonucleotide pairs shown in Tables B1-B36 , set forth in SEQ ID NOS:59-33,596.

In yet another aspect, the present ~~invention~~disclosure provides a topical ophthalmic pharmaceutical composition for non-invasive treatment of an ocular disease associated with pathological abnormalities/changes in the tissues of the visual system, comprising: (a) a therapeutically effective amount of at least one siRNA to a target gene in the retina of the subject, wherein the target gene is set forth in any one of SEQ ID NO:1- 58, and (b) a pharmaceutically acceptable excipient or carrier or mixture thereof. In preferred embodiments the at least one siRNA is a chemically modified. In various embodiments the siRNA sense and antisense oligonucleotides are selected from sense and corresponding antisense oligonucleotide pairs shown in Tables B1-B36, set forth in SEQ ID NOS:59-33,596.

According to another aspect, the present ~~invention~~disclosure is directed to a topical ophthalmic pharmaceutical composition for use in treating a subject afflicted with ocular disease associated with death of retinal ganglion cells, which comprises: (a) a therapeutically effective amount of at least one siRNA to a target gene in the retina of the subject,

wherein the target gene is set forth in any one of SEQ ID NO:1- 58, and (b) a pharmaceutically acceptable excipient or carrier or mixture thereof. In preferred embodiments the at least one siRNA is a chemically modified. In various embodiments the siRNA sense and antisense oligonucleotides are selected from sense and corresponding antisense oligonucleotide pairs shown in Tables B1-B36, set forth in SEQ ID NOS:59-33,596.

In various embodiments the ocular disease is selected from a group comprising glaucoma, dry eye, diabetic retinopathy (DR), diabetic macular edema (DME), age related macular degeneration (AMD), optic neuritis, central retinal vein occlusion, brunch retinal vein occlusion, ischemic optic neuropathy, optic nerve injury, retinopathy of prematurity (ROP) or retinitis pigmentosa (RP),retinal ganglion degeneration, macular degeneration, hereditary optic neuropathy, metabolic optic neuropathy, neuropathy due to a toxic agent or that caused by adverse drug reactions or vitamin deficiency; and the composition is formulated as a cream, a foam, a paste, an ointment, an emulsion, a liquid solution, an eye drop, a gel, spray, a suspension, a microemulsion, microspheres, microcapsules, nanospheres, nanoparticles, lipid vesicles, liposomes, polymeric vesicles, a patch, a biological insert. In a preferred embodiment the composition is formulated as an eye drop.

In another aspect the ~~invention~~disclosure is directed to a packaged pharmaceutical preparation, comprising: (a) a pharmaceutical composition according to the invention in a container; and (b) instructions for using the composition to treat an ocular disease. In various embodiments the pharmaceutical composition according to present ~~invention~~disclosure comprises a therapeutically effective amount of at least one siRNA to a target gene in the retina of the subject suffering from an ocular disease. In preferred embodiments the at least one siRNA is a chemically modified. In some embodiments the target gene is set forth in any one of SEQ ID NO:1- 58. In various embodiments the siRNA sense and antisense oligonucleotides are selected from sense and corresponding antisense oligonucleotides set forth in SEQ ID NOS:59-33,596. In one particular embodiment according to this aspect of the ~~invention~~disclosure, the pharmaceutical composition is for non-invasive treatment of an ocular disease associated with loss of a retinal ganglion cell in a subject. In another particular embodiment according to this aspect the ~~invention~~disclosure, the pharmaceutical composition is for non-invasive treatment of an ocular disease associated with pathological abnormalities/changes in the tissues of the visual system. In yet another particular embodiment according to this aspect the ~~invention~~disclosure, the pharmaceutical

composition is for use in treating a subject afflicted with ocular disease associated with death of retinal ganglion cells.

According to another aspect, the ~~invention~~disclosure is directed to use of a pharmaceutical composition according to the ~~invention~~disclosure in the manufacture of a medicament for promoting retinal ganglion cell survival in a subject. In various embodiments the pharmaceutical composition according to present ~~invention~~disclosure comprises a therapeutically effective amount of at least one siRNA to a target gene in the retina of the subject suffering from an ocular disease. In preferred embodiments the at least one siRNA is a chemically modified. In some embodiments the target gene is set forth in any one of SEQ ID NO:1- 58. In various embodiments the siRNA sense and antisense oligonucleotides are selected from sense and corresponding antisense oligonucleotide pairs shown in Tables B1-B36 , set forth in SEQ ID NOS:59-33,596. In one particular embodiment according to this aspect the ~~invention~~disclosure the pharmaceutical composition is for non-invasive treatment of an ocular disease associated with loss of a retinal ganglion cell in a subject. In another particular embodiment according to this aspect the ~~invention~~disclosure the pharmaceutical composition is for non-invasive treatment of an ocular disease associated with pathological abnormalities/changes in the tissues of the visual system. In yet another particular embodiment according to this aspect the ~~invention~~disclosure the pharmaceutical composition is for use in treating a subject afflicted with ocular disease associated with death of retinal ganglion cells.

In some embodiments the composition includes a viscosity enhancing agent. A viscosity enhancing agent is selected from for example a hydrophilic polymer including cellulose and cellulose derivatives methylcellulose and methylcellulose derivatives. Such agents include methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose, derivatives thereof, combinations thereof and and their salts. In some embodiments the viscosity enhancing agent is methylcellulose. In certain embodiments the viscosity enhancing agent is provided at a concentration of about 0.01% to about 4%, in other embodiments the viscosity enhancing agent is provided at a concentration of about 0.1% to about 3%, or at a concentration of about 0.5% to about 2%.

In some embodiments the composition includes an agent providing osmotic balance, or a surfactant. Such agents include glycerol, ethylene glycol, poly(ethylene glycol), propylene glycol, sorbitol, mannitol, monosaccharide, disaccharides and oligosaccharides.

The present ~~invention~~disclosure further provides a method of treating glaucoma in a subject in need of treatment that comprises topically (non-invasively) administering to the surface of the eye of the subject a therapeutically effective amount of at least one siRNA to a target gene in the eye of the subject, in an amount effective to treat glaucoma. In certain preferred embodiments the siRNA chemically modified siRNA. In certain embodiments the at least one siRNA inhibits expression of at least one gene expressed in the retina of the subject's eye. In certain embodiments inhibition of at least one gene confers upon the eye neuroprotective properties. In certain embodiments the at least one gene is selected from a list in Table A1 transcribed into mRNA set forth in SEQ ID NO:1-35. In certain preferred embodiments the gene is selected from CASP2 (SEQ ID NO:1-2), ASPP1 (SEQ ID NO:4), TP53BP2 (SEQ ID NO:6-7), BNIP3 (SEQ ID NO:12), RTP801L (SEQ ID NO:14), ACHE (SEQ ID NO:19-20), ADRB1 (SEQ ID NO:21) and CAPNS1 (SEQ ID NO:28-29). In various embodiments the gene is set forth in SEQ ID NOS:1-2. In some embodiments the siRNA sense and antisense strands are selected from any one of sequences set forth in SEQ ID NOS:8515-9516.

The present ~~invention~~disclosure further provides a method of treating dry-eye in a subject in need thereof, which comprises topically (non-invasively) applying to the surface of the eye of the subject a therapeutically effective amount of at least one siRNA which inhibits expression of at least one gene expressed in the eye of the subject in an amount effective to reduce the symptoms of dry eye. In certain preferred embodiments the siRNA is chemically modified siRNA. In certain embodiments the at least one gene is expressed in the lacrimal gland in the subject. In certain embodiments the at least gene is selected from Table A2 set forth in any one of SEQ ID NO: 5, SEQ ID NO:8-10, SEQ ID NO:26 - 27 and SEQ ID NO:30 - 44. In some embodiments the gene is selected from FAS, FAS ligand (FASL), p53, LRDD, PARP1, AIF (apoptosis inducing factor), NOS1, NOS2A, XIAP and SHC1-SHC. In certain preferred embodiments the gene is transcribed into mRNA set forth in any one of SEQ ID NO:36 - SEQ ID NO:44. In some embodiments the siRNA sense and antisense strands are selected from any one of sequences in Tables 16-17 set forth in SEQ ID NOS: 13,225-15,224.

The present ~~invention~~disclosure further provides a method of treating AMD, DR or DME in a subject in need thereof, which comprises topically (non-invasively) administering to the surface of the eye of the subject a therapeutically effective amount of at least one siRNA which inhibits expression of at least one gene expressed in the eye in the subject in an

amount effective to reduce the symptoms of AMD, DR or DME. In certain preferred embodiments the siRNA is chemically modified siRNA. In certain embodiments the at least one siRNA inhibits expression of at least one gene expressed in the choroid in the subject's eye. In certain embodiments the at least one target ocular mRNA listed in Table A3, set forth in any one of SEQ ID NOS:1-2, 3, 5, 6-7, 8-10, 12, 13, 24-25, 26-27, 30-35, 45-53 . In certain preferred embodiments the siRNA targets CTSD, RTP801 and BNIP3. In certain preferred embodiments the disorder is DR and the siRNA targets mRNA set forth in SEQ ID NOS:48-53.

In a further embodiment the eye disorder is Retinitis pigmentosa (RP). Thus, the present ~~invention~~disclosure provides a method of attenuating expression of a target ocular mRNA in the eye of a subject suffering from RP. The method comprises topically (non-invasively) applying to the surface of the eye of the subject a therapeutically effective amount of at least one siRNA to a target gene in the eye of the subject. In certain preferred embodiments the siRNA is chemically modified siRNA. In certain embodiments attenuating expression of at least one target gene (target ocular mRNA) is effective to treat RP. In certain embodiments attenuation of at least one target ocular mRNA is effective to reduce the symptoms of RP. In certain embodiments the at least one target ocular mRNA is product of a gene selected from a gene listed in Table A4 which is transcribed into mRNA set forth in any one of SEQ ID NOS: 3, 14, 26-35, 54-57. In some embodiments the target ocular mRNA is product of a gene selected from the group consisting of CASP1, CASP3, CASP12, RTP801, RTP801L, CAPNS1, PARP1, AIF, NOS1, NOS2, XIAP and SHC1-SHC. In certain preferred embodiments the siRNA targets mRNA set forth in SEQ ID NOS:56-57.

In various embodiments the at least one siRNA is chemically modified. In various embodiments the at least one siRNA comprises a sufficient number of consecutive nucleotides having a sequence of sufficient homology to a nucleic acid sequence present within the target mRNA to hybridize to the mRNA and attenuate expression of the mRNA in the eye of the subject.

In various embodiments the at least one siRNA comprises a sufficient number of consecutive nucleotides having a sequence of sufficient homology to a nucleic acid sequence present within the gene to hybridize to the gene and reduce or inhibit expression of the gene in the eye of the subject.

In one aspect, there is provided a double stranded RNA compound having the structure:

5' iB – GCCAGAAUGUGGAACUCCU 3' (sense strand; SEQ ID NO: 9015)

3' CGGUCUUACACCUUGAGGA 5' (antisense strand; SEQ ID NO: 9516)

wherein each A, C, U, and G is a ribonucleotide and each consecutive ribonucleotide is joined to the next ribonucleotide by a phosphodiester bond;

wherein the sense strand comprises, counting from the 5' terminus, an unmodified ribonucleotide at positions 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 and 19, a L-deoxycytidine at position 18, and an inverted abasic 5' cap; and

wherein the antisense strand comprises, counting from the 5' terminus, a 2'-O-Me sugar modified ribonucleotide at positions 2, 4, 6, 8, 11, 13, 15, 17 and 19 and an unmodified ribonucleotide at positions 1, 3, 5, 7, 9, 10, 12, 14, 16 and 18.

In another aspect, there is provided the use of the compound as defined above in the manufacture of a medicament for the treatment of an ocular disease, an ocular disorder, an ocular injury, a visual field loss; or for providing ocular neuroprotection.

In another aspect, there is provided a composition comprising the compound as defined above and a pharmaceutically acceptable excipient or carrier or mixture thereof.

In another aspect, there is provided a composition comprising the compound as defined above in an amount effective to down-regulating expression of a CASP2 gene in an ocular cell selected from a group consisting of an acinar cell of the lacrimal gland, a ductal cell of the lacrimal gland, a retinal ganglion cell (RGC), a retinal pigment epithelial (RPE) cell, a choroidal cell, a corneal cell, a cell of the ciliary process and a cell of the trabecular meshwork, or a combination thereof.