

INCREASING ADHESION BETWEEN VITREOUS AND RETINA

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] Pursuant to 35 U.S.C. § 119(e), this application claims priority to the filing date of United States Provisional Patent Application Serial No. 63/472,722 filed June 13, 2023, the disclosure of each of which is herein incorporated by reference in their entirety.

BACKGROUND

[0002] Retinal detachment (RD) occurs when the neurosensory retina separates from the retinal pigment epithelium and underlying vascular supply, the choroid. Rhegmatogenous retinal detachment (RRD), occurs when a break (tear) in the retina allows vitreous fluid to flow across the break into the subretinal space. Despite surgical advances, a delay in diagnosis, and treatment can lead to permanent vision loss. While overall the incidence is 1/10,000 people per year, this can much higher in individuals who have established risk factors including high myopia, previous ocular surgery, or history retinal tears in the other eye. While patients with lattice degeneration or retinal tears can be treated prophylactically with laser photocoagulation to reduce the risk of RRD, there is no way to reliably prevent RRD in these high-risk patients.

[0003] An event occurring prior to RRD is posterior vitreous detachment (PVD). PVD occurs when the vitreous gel becomes untethered (detached) from the back of the eye. PVD allows the vitreous to move freely and “whip” as the eye moves; this generates outsized tractional forces on remaining anterior vitreo-retinal attachments that can tear the retina, leading to RRD.

[0004] Preventing posterior vitreous release would prevent generation of outsized tractional forces due to the free motion of the vitreous and thereby prevent retinal tearing and detachment.

[0005] There is currently no therapy or prophylactic for the problem of loss of adhesion between the vitreous and the retina that leads to PVD. Methods for increasing this adhesion and prevent complete PVD would represent an advancement in the art. Herein, a solution to this problem, among others, is presented.

SUMMARY

[0006] The present disclosure relates generally to methods of increasing the adhesion between vitreous and retina.

[0007] In one aspect, the invention provides a method of increasing adhesion between vitreous and retina in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thereby increasing adhesion between vitreous and retina in the eye of the mammal.

[0008] In one aspect, the invention provides a method of increasing adhesion between vitreous and retina in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI in which the photosensitizer has accumulated, with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thereby increasing adhesion between vitreous and retina in the eye of the mammal.

[0009] The foregoing summary is illustrative only and is not intended to be in any way limiting. In addition to the illustrative embodiments and features described herein, further aspects, embodiments, objects and features of the disclosure will become fully apparent from the drawings and the detailed description and the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] The features of the present disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings.

[0011] **FIG 1** shows a plasmin eye injection strategy.

[0012] **FIG 2** shows average vitrector vacuum versus maximum mass lifted by aspiration.

[0013] FIG 3 shows the effect of plasmin concentration injected on the average minimum vacuum needed to induce a PVD.

[0014] FIG 4 shows PVD data for eyes treated with plasmin, glutaraldehyde, a MetB 1:100 solution, and a MetB 1:1000 solution.

[0015] FIG 5 shows power of 660nm flashlight measured after going through each condition.

[0016] FIG 6 shows funneling light at the bottom of the beaker.

[0017] FIG 7 shows intensity of laser light in relation to power measured.

[0018] FIG 8 shows average minimum pressure needed to induce PVD per category.

DETAILED DESCRIPTION OF THE DISCLOSURE

I. Definitions

[0019] Unless otherwise defined, all terms of art, notations, and other scientific terms or terminology used herein are intended to have the meanings commonly understood by those of skill in the art to which this application pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not necessarily be construed to represent a substantial difference over what is generally understood in the art. Many of the techniques and procedures described or referenced herein are well understood and commonly employed using conventional methodology by those skilled in the art.

[0020] The singular form “a”, “an”, and “the” include plural references unless the context clearly dictates otherwise. For example, the term “a cell” includes one or more cells, comprising mixtures thereof. “A and/or B” is used herein to include all of the following alternatives: “A”, “B”, “A or B”, and “A and B”.

[0021] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the disclosure. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the disclosure, subject to any specifically excluded limit in the stated range. Where the stated range includes one

or both of the limits, ranges excluding either or both of those included limits are also included in the disclosure.

[0022] Certain ranges are presented herein with numerical values being preceded by the term “about.” The term “about” is used herein to provide literal support for the exact number that it precedes, as well as a number that is near to or approximately the number that the term precedes. In determining whether a number is near to or approximately a specifically recited number, the near or approximating unrecited number may be a number which, in the context in which it is presented, provides the substantial equivalent of the specifically recited number. If the degree of approximation is not otherwise clear from the context, “about” means either within plus or minus 10% of the provided value, or rounded to the nearest significant figure, in all cases inclusive of the provided value. In some embodiments, the term “about” indicates the designated value $\pm$ up to 10%, up to $\pm$ 5%, or up to $\pm$ 1%.

[0023] Photosensitizer, as used herein, refers to a molecule that, upon activation by light, facilitates crosslinking between biological components in the vitreous and biological components in the retina. In certain embodiments, the crosslinking is between a glycoprotein (such as a glyco-collagen) in the vitreous and a glycoprotein (such as a glyco-collagen) in the retina. Crosslinking cortical vitreous to inner surface of retina, the internal limiting membrane (ILM). In certain embodiments, the crosslinking is between a saccharide moiety on a glycoprotein (such as a glyco-collagen) in the vitreous and a saccharide moiety on a glycoprotein (such as a glyco-collagen) in the retina. In certain embodiments, the crosslinking is between a saccharide moiety on a glycoprotein (such as a glyco-collagen) in the vitreous and a saccharide moiety on a glycoprotein (such as a glyco-collagen) in the retina. In certain embodiments, the crosslinking is between an amino acid moiety on a glycoprotein (such as a glyco-collagen) in the vitreous and an amino acid moiety on a glycoprotein (such as a glyco-collagen) in the retina. In certain embodiments, the crosslinking is of the vitreous gel to prevent liquefaction.

[0024] Adhesion, as used herein, refers to non-covalent interactions (hydrogen bonds, van der Waals interactions, ionic bonds, and/or hydrophobic bonds) as well as covalent interactions.

[0025] Crosslinking, as used herein, refers to the process of chemically joining two or more molecules by a covalent bond.

[0026] Vitreoretinal interface (VRI), as used herein, refers to the junction between vitreous and retina. In certain embodiments, the vitreoretinal interface refers to the junction between cortical vitreous and retina. In certain embodiments, the vitreoretinal interface refers to the junction between cortical vitreous and internal limiting membrane (ILM) of the retina.

[0027] MetB or Met B, as used herein, refers to methylene blue.

[0028] It is understood that aspects and embodiments of the disclosure described herein include "comprising", "consisting", and "consisting essentially of" aspects and embodiments. As used herein, "comprising" is synonymous with "including", "containing", or "characterized by", and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. As used herein, "consisting of" excludes any elements, steps, or ingredients not specified in the claimed composition or method. As used herein, "consisting essentially of" does not exclude materials or steps that do not materially affect the basic and novel characteristics of the claimed composition or method. Any recitation herein of the term "comprising", particularly in a description of components of a composition or in a description of steps of a method, is understood to encompass those compositions and methods consisting essentially of and consisting of the recited components or steps.

[0029] All genes, gene names, and gene products disclosed herein are intended to correspond to homologs from any species for which the compositions and methods disclosed herein are applicable. Thus, the terms include, but are not limited to genes and gene products from humans and mice. It is understood that when a gene or gene product from a particular species is disclosed, this disclosure is intended to be exemplary only, and is not to be interpreted as a limitation unless the context in which it appears clearly indicates. Thus, for example, for the genes or gene products disclosed herein, which in some embodiments relate to mammalian nucleic acid and amino acid sequences, are intended to encompass homologous and/or orthologous genes and gene products from other animals including, but not limited to other mammals, fish, amphibians, reptiles, and birds. In some embodiments, the genes, nucleic acid sequences, amino acid sequences, peptides, polypeptides and proteins are human. The term "gene" is also intended to include variants thereof.

[0030] It is appreciated that certain features of the disclosure, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single

embodiment. Conversely, various features of the disclosure, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination. All combinations of the embodiments pertaining to the disclosure are specifically embraced by the present disclosure and are disclosed herein just as if each and every combination was individually and explicitly disclosed. In addition, all sub-combinations of the various embodiments and elements thereof are also specifically embraced by the present disclosure and are disclosed herein just as if each and every such sub-combination was individually and explicitly disclosed herein.

II. Methods

II. a) Method of increasing adhesion between vitreous and retina

[0031] In one aspect, the invention provides a method of increasing adhesion between vitreous and retina in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI, with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thereby increasing adhesion between vitreous and retina in the eye of the mammal. In one aspect, the invention provides a method of increasing adhesion between vitreous and retina in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI in which the photosensitizer has accumulated, with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thereby increasing adhesion between vitreous and retina in the eye of the mammal. In an exemplary embodiment, the irradiating is with light of a wavelength by which the photosensitizer induces crosslinking between the vitreous and the retina of the eye of the mammal. In an exemplary embodiment, the irradiating is with light of a wavelength by which the photosensitizer initiates crosslinking between the vitreous and the retina of the eye of the mammal. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the retina. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the internal limiting membrane of the retina. In an exemplary embodiment, the increasing adhesion results in an increase in the tensile strength between the vitreous and the retina.

II. b) Method of increasing attachment between vitreous and retina

[0032] In one aspect, the invention provides a method of increasing attachment between vitreous and retina in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thereby increasing attachment between vitreous and retina in the eye of the mammal. In one aspect, the invention provides a method of increasing attachment between vitreous and retina in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI in which the photosensitizer has accumulated, with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thereby increasing attachment between vitreous and retina in the eye of the mammal. In an exemplary embodiment, the irradiating is with light of a wavelength by which the photosensitizer induces crosslinking between the vitreous and the retina of the eye of the mammal. In an exemplary embodiment, the irradiating is with light of a wavelength by which the photosensitizer initiates crosslinking between the vitreous and the retina of the eye of the mammal. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the retina. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the internal limiting membrane of the retina. In an exemplary embodiment, the increasing attachment results in an increase in the tensile strength between the vitreous and the retina.

II. c) Method of increasing covalent attachment between vitreous and retina

[0033] In one aspect, the invention provides a method of increasing covalent attachment between vitreous and retina in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI, with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thereby increasing covalent attachment between vitreous and retina in the eye of the mammal. In one aspect, the invention provides a method of increasing covalent attachment between vitreous and retina in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI in

which the photosensitizer has accumulated, with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thereby increasing covalent attachment between vitreous and retina in the eye of the mammal. In an exemplary embodiment, the irradiating is with light of a wavelength by which the photosensitizer induces crosslinking between the vitreous and the retina of the eye of the mammal. In an exemplary embodiment, the irradiating is with light of a wavelength by which the photosensitizer initiates crosslinking between the vitreous and the retina of the eye of the mammal. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the retina. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the internal limiting membrane of the retina. In an exemplary embodiment, the increasing covalent attachment results in an increase in the tensile strength between the vitreous and the retina.

II. d) Method of introducing covalent attachment between vitreous and retina

[0034] In one aspect, the invention provides a method of introducing covalent attachment between vitreous and retina in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thereby introducing covalent attachment between vitreous and retina in the eye of the mammal. In one aspect, the invention provides a method of introducing covalent attachment between vitreous and retina in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI in which the photosensitizer has accumulated, with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thereby introducing covalent attachment between vitreous and retina in the eye of the mammal. In an exemplary embodiment, the irradiating is with light of a wavelength by which the photosensitizer induces crosslinking between the vitreous and the retina of the eye of the mammal. In an exemplary embodiment, the irradiating is with light of a wavelength by which the photosensitizer initiates crosslinking between the vitreous and the retina of the eye of the mammal. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the retina. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the internal limiting membrane of the

retina. In an exemplary embodiment, the introducing covalent attachment results in an increase in the tensile strength between the vitreous and the retina.

II. e) Method of covalently attaching vitreous and retina

[0035] In one aspect, the invention provides a method of covalently attaching vitreous and retina in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thereby covalently attaching vitreous and retina in the eye of the mammal. In one aspect, the invention provides a method of covalently attaching vitreous and retina in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI in which the photosensitizer has accumulated, with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thereby covalently attaching vitreous and retina in the eye of the mammal. In an exemplary embodiment, the irradiating is with light of a wavelength by which the photosensitizer induces crosslinking between the vitreous and the retina of the eye of the mammal. In an exemplary embodiment, the irradiating is with light of a wavelength by which the photosensitizer initiates crosslinking between the vitreous and the retina of the eye of the mammal. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the retina. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the internal limiting membrane of the retina. In an exemplary embodiment, the covalently attaching results in an increase in the tensile strength between the vitreous and the retina.

II. f) Method of covalently attaching vitreous collagen and retina collagen

[0036] In one aspect, the invention provides a method of covalently attaching vitreous collagen and retina collagen in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI with light of a wavelength by which crosslinking occurs between the vitreous collagen and the retina collagen, thereby covalently attaching vitreous collagen and retina collagen in the eye of the mammal. In one aspect, the invention provides a method of covalently attaching vitreous collagen and retina collagen in an eye of a

mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI in which the photosensitizer has accumulated, with light of a wavelength by which crosslinking occurs between the vitreous collagen and the retina collagen, thereby covalently attaching vitreous collagen and retina collagen in the eye of the mammal. In an exemplary embodiment, the irradiating is with light of a wavelength by which the photosensitizer induces crosslinking between the vitreous collagen and the retina collagen of the eye of the mammal. In an exemplary embodiment, the irradiating is with light of a wavelength by which the photosensitizer initiates crosslinking between the vitreous collagen and the retina collagen of the eye of the mammal. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the retina. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the internal limiting membrane of the retina. In an exemplary embodiment, the covalently attaching results in an increase in the tensile strength between the vitreous and the retina.

II. g) Method of covalently attaching vitreous glycoproteins and retina glycoproteins

[0037] In one aspect, the invention provides a method of covalently attaching vitreous glycoproteins and retina glycoproteins in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI with light of a wavelength by which crosslinking occurs between the vitreous glycoproteins and the retina glycoproteins, thereby covalently attaching the vitreous glycoproteins and the retina glycoproteins in the eye of the mammal. In one aspect, the invention provides a method of covalently attaching vitreous glycoproteins and retina glycoproteins in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI in which the photosensitizer has accumulated, with light of a wavelength by which crosslinking occurs between the vitreous glycoproteins and the retina glycoproteins, thereby covalently attaching the vitreous glycoproteins and the retina glycoproteins in the eye of the mammal. In an exemplary embodiment, the irradiating is with light of a wavelength by which the photosensitizer induces crosslinking between the vitreous glycoproteins and the retina glycoproteins of the eye of the mammal. In an exemplary embodiment, the irradiating is with

light of a wavelength by which the photosensitizer initiates crosslinking between the vitreous glycoproteins and the retina glycoproteins of the eye of the mammal. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the retina. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the internal limiting membrane of the retina. In an exemplary embodiment, the covalently attaching results in an increase in the tensile strength between the vitreous and the retina.

II. h) Method of treating lack of adhesion between vitreous and retina

[0038] In one aspect, the invention provides a method of treating lack of adhesion between vitreous and retina in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thereby treating lack of adhesion between vitreous and retina in the eye of the mammal. In one aspect, the invention provides a method of treating lack of adhesion between vitreous and retina in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI in which the photosensitizer has accumulated, with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thereby treating lack of adhesion between vitreous and retina in the eye of the mammal. In an exemplary embodiment, the irradiating is with light of a wavelength by which the photosensitizer induces crosslinking between the vitreous and the retina of the eye of the mammal. In an exemplary embodiment, the irradiating is with light of a wavelength by which the photosensitizer initiates crosslinking between the vitreous and the retina of the eye of the mammal. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the retina. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the internal limiting membrane of the retina. In an exemplary embodiment, the treating results in an increase in the tensile strength between the vitreous and the retina. In an exemplary embodiment, the method further comprises diagnosing the mammal (such as a human) as being in need of the treating. In an exemplary embodiment, the method further comprises diagnosing the mammal (such as a human) with an ocular condition by which this method can treat. In an exemplary embodiment, the method further comprises diagnosing the mammal (such as a human) with an ocular condition described herein. In an exemplary

embodiment, the mammal (such as a human) lacks adhesion between vitreous and retina in a first eye, and the treating is directed to the first eye. In an exemplary embodiment, the mammal (such as a human) lacks adhesion between vitreous and retina in a first and second eye, and the treating is directed to the first eye and/or second eye.

II. i) Method of treating decreasing adhesion between vitreous and retina

[0039] In one aspect, the invention provides a method of treating decreasing adhesion between vitreous and retina in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thereby treating decreasing adhesion between vitreous and retina in the eye of the mammal. In one aspect, the invention provides a method of treating decreasing adhesion between vitreous and retina in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI in which the photosensitizer has accumulated, with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thereby treating decreasing adhesion between vitreous and retina in the eye of the mammal. In an exemplary embodiment, the irradiating is with light of a wavelength by which the photosensitizer induces crosslinking between the vitreous and the retina of the eye of the mammal. In an exemplary embodiment, the irradiating is with light of a wavelength by which the photosensitizer initiates crosslinking between the vitreous and the retina of the eye of the mammal. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the retina. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the internal limiting membrane of the retina. In an exemplary embodiment, the treating results in an increase in the tensile strength between the vitreous and the retina. In an exemplary embodiment, the method further comprises diagnosing the mammal (such as a human) as being in need of the treating. In an exemplary embodiment, the method further comprises diagnosing the mammal (such as a human) with an ocular condition by which this method can treat. In an exemplary embodiment, the method further comprises diagnosing the mammal (such as a human) with an ocular condition described herein. In an exemplary embodiment, the mammal (such as a human) has decreasing adhesion between vitreous and retina in a first eye, and the treating is directed to the first eye. In an

exemplary embodiment, the mammal (such as a human) has decreasing adhesion between vitreous and retina in a first and second eye, and the treating is directed to the first eye and/or second eye.

II. j) Method of preventing ocular conditions of the eye

[0040] In another aspect, the invention is a method of preventing an ocular condition in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thereby preventing the ocular condition in the eye of the mammal. In another aspect, the invention is a method of preventing an ocular condition in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI in which the photosensitizer has accumulated, with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thereby preventing the ocular condition in the eye of the mammal. In an exemplary embodiment, the ocular condition is posterior vitreous detachment, retinal tear, rhegmatogenous retinal detachment, macular hole, vitreomacular traction, epiretinal membrane, or a vitreous floater. In an exemplary embodiment, the ocular condition is complete posterior vitreous detachment, retinal tear, rhegmatogenous retinal detachment, macular hole, epiretinal membrane, or a vitreous floater. In an exemplary embodiment, the ocular condition is reduced adhesion between vitreous and retina. In an exemplary embodiment, the ocular condition is decreased adhesion between vitreous and retina. In an exemplary embodiment, the ocular condition is lack of adhesion between vitreous and retina. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the retina. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the internal limiting membrane of the retina. In an exemplary embodiment, the method further comprises diagnosing the mammal (such as a human) as being in need of the preventing. In an exemplary embodiment, the method further comprises diagnosing the mammal (such as a human) with an ocular condition described herein. In an exemplary embodiment, the method further comprises diagnosing the mammal (such as a human) with an ocular condition in a first eye by which this method can prevent in the second eye. In an exemplary embodiment, the method further comprises diagnosing the mammal (such as a human) with posterior vitreous

detachment in a first eye, and the method is to prevent posterior vitreous detachment in the second eye. In an exemplary embodiment, the method further comprises diagnosing the mammal (such as a human) with retinal tear in a first eye, and the method is to prevent retinal tear in the second eye.

[0041] In an exemplary embodiment, when the ocular condition is posterior vitreous detachment, the selective region of the VRI comprises an area nasal to the optic nerve. In an exemplary embodiment, when the ocular condition is retinal tear, the selective region of the VRI comprises an area nasal to the optic nerve. In an exemplary embodiment, when the ocular condition is rhegmatogenous retinal detachment, the selective region of the VRI comprises an area nasal to the optic nerve. In an exemplary embodiment, when the ocular condition is macular hole, the selective region of the VRI comprises the macula. In an exemplary embodiment, when the ocular condition is vitreomacular traction, the selective region of the VRI comprises the macula. In an exemplary embodiment, when the ocular condition is epiretinal membrane, the selective region of the VRI comprises the macula. In an exemplary embodiment, when the ocular condition is a vitreous floater, the selective region of the VRI comprises an area nasal to the optic nerve. In an exemplary embodiment, the preventing results in an increase in the tensile strength between the vitreous and the retina.

[0042] In an exemplary embodiment, when the ocular condition is posterior vitreous detachment, the selective region of the VRI in which the photosensitizer has accumulated, comprises an area nasal to the optic nerve. In an exemplary embodiment, when the ocular condition is retinal tear, the selective region of the VRI in which the photosensitizer has accumulated, comprises an area nasal to the optic nerve. In an exemplary embodiment, when the ocular condition is rhegmatogenous retinal detachment, the selective region of the VRI in which the photosensitizer has accumulated, comprises an area nasal to the optic nerve. In an exemplary embodiment, when the ocular condition is macular hole, the selective region of the VRI in which the photosensitizer has accumulated, comprises the macula. In an exemplary embodiment, when the ocular condition is vitreomacular traction, the selective region of the VRI in which the photosensitizer has accumulated, comprises the macula. In an exemplary embodiment, when the ocular condition is epiretinal membrane, the selective region of the VRI in which the photosensitizer has accumulated, comprises the macula. In an exemplary embodiment, when the ocular condition is a vitreous floater, the selective region of the VRI in which the photosensitizer has

accumulated, comprises an area nasal to the optic nerve. In an exemplary embodiment, the preventing results in an increase in the tensile strength between the vitreous and the retina.

II. k) Method of preventing an ocular condition through effecting targeted enhanced adhesion

[0043] In another aspect, the invention is a method of preventing an ocular condition through effecting targeted enhanced adhesion between vitreous and retina in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thereby preventing an ocular condition through creating enhanced adhesion between vitreous and retina in the eye of the mammal. In another aspect, the invention is a method of preventing an ocular condition through effecting targeted enhanced adhesion between vitreous and retina in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI in which the photosensitizer has accumulated, with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thereby preventing an ocular condition through creating enhanced adhesion between vitreous and retina in the eye of the mammal. In an exemplary embodiment, the ocular condition is posterior vitreous detachment, retinal tear, rhegmatogenous retinal detachment, macular hole, vitreomacular traction, epiretinal membrane, or a vitreous floater. In an exemplary embodiment, the ocular condition is complete posterior vitreous detachment, retinal tear, rhegmatogenous retinal detachment, macular hole, epiretinal membrane, or a vitreous floater. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the retina. In an exemplary embodiment, the crosslinking occurs between the cortical vitreous and the internal limiting membrane of the retina. In an exemplary embodiment, the method further comprises diagnosing the mammal (such as a human) as being in need of the preventing. In an exemplary embodiment, the method further comprises diagnosing the mammal (such as a human) with an ocular condition described herein. In an exemplary embodiment, the method further comprises diagnosing the mammal (such as a human) with an ocular condition in a first eye by which this method can prevent in the second eye. In an exemplary embodiment, the method further comprises diagnosing the mammal (such as a human) with posterior vitreous detachment in a first eye, and the method is to prevent posterior vitreous detachment in the second eye. In an

exemplary embodiment, the method further comprises diagnosing the mammal (such as a human) with retinal tear in a first eye, and the method is to prevent retinal tear in the second eye.

[0044] In an exemplary embodiment, when the ocular condition is posterior vitreous detachment, the selective region of the VRI comprises an area nasal to the optic nerve. In an exemplary embodiment, when the ocular condition is retinal tear, the selective region of the VRI comprises an area nasal to the optic nerve. In an exemplary embodiment, when the ocular condition is rhegmatogenous retinal detachment, the selective region of the VRI comprises an area nasal to the optic nerve. In an exemplary embodiment, when the ocular condition is macular hole, the selective region of the VRI comprises the macula. In an exemplary embodiment, when the ocular condition is vitreomacular traction, the selective region of the VRI comprises the macula. In an exemplary embodiment, when the ocular condition is epiretinal membrane, the selective region of the VRI comprises the macula. In an exemplary embodiment, when the ocular condition is a vitreous floater, the selective region of the VRI comprises an area nasal to the optic nerve. In an exemplary embodiment, the preventing results in an increase in the tensile strength between the vitreous and the retina.

[0045] In an exemplary embodiment, when the ocular condition is posterior vitreous detachment, the selective region of the VRI in which the photosensitizer has accumulated, comprises an area nasal to the optic nerve. In an exemplary embodiment, when the ocular condition is retinal tear, the selective region of the VRI in which the photosensitizer has accumulated, comprises an area nasal to the optic nerve. In an exemplary embodiment, when the ocular condition is rhegmatogenous retinal detachment, the selective region of the VRI in which the photosensitizer has accumulated, comprises an area nasal to the optic nerve. In an exemplary embodiment, when the ocular condition is macular hole, the selective region of the VRI in which the photosensitizer has accumulated, comprises the macula. In an exemplary embodiment, when the ocular condition is vitreomacular traction, the selective region of the VRI in which the photosensitizer has accumulated, comprises the macula. In an exemplary embodiment, when the ocular condition is epiretinal membrane, the selective region of the VRI in which the photosensitizer has accumulated, comprises the macula. In an exemplary embodiment, when the ocular condition is a vitreous floater, the selective region of the VRI in which the photosensitizer has accumulated, comprises an area nasal to the optic nerve. In an exemplary embodiment, the preventing results in an increase in the tensile strength between the vitreous and the retina.

II. l) Method of increasing adhesion with light and without a photosensitizer between vitreous and retina

[0046] In another aspect, the invention is a method of increasing adhesion between vitreous and retina in an eye of a mammal, comprising: irradiating a selective region of the vitreoretinal interface (VRI) of the eye of the mammal with light of a wavelength from about 650 nm and about 670 nm by which crosslinking occurs between the vitreous and the retina, wherein a photosensitizer is not present in the eye of the mammal, thereby increasing the adhesion between vitreous and retina in the eye of the mammal.

II. m) Method of testing for increased adhesion between vitreous and retina

[0047] In another aspect, the invention is a method of testing for a photosensitizer that increases adhesion (such as covalent attachment such as crosslinking) between vitreous and retina in an eye of a mammal, comprising: a) administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); b) irradiating a selective region of the VRI with light of a wavelength by which crosslinking occurs between the vitreous and the retina, thus creating a tested eye; c) administering a protease to the VRI; d) testing the adhesion between the vitreous and the retina; e) comparing the results of step d) with results obtained for a second eye, thereby testing for a photosensitizer that increases adhesion (such as covalent attachment such as crosslinking) between vitreous and retina in an eye of a mammal. In an exemplary embodiment, the testing is *ex vivo*. In an exemplary embodiment, the tested eye is *ex vivo*, and the second eye is *ex vivo*. In an exemplary embodiment, if the adhesion is increased in the tested eye as compared with the second eye, then the photosensitizer increases adhesion between vitreous and retina in the eye of the mammal. In an exemplary embodiment, the protease is a serine protease. In an exemplary embodiment, the protease is plasmin. The amount of protease applied to the eye ranges from about 0.5U and about 5U. The amount of protease applied to the eye ranges from 2U and 5U. In an exemplary embodiment, the testing comprises administering a vacuum described herein. In an exemplary embodiment, the testing comprises determining the average minimum vacuum needed to induce posterior vitreous detachment in the eye. In an exemplary embodiment, wherein the results of step d) for the second eye comprise determining the average minimum vacuum needed to induce posterior vitreous detachment in the second eye, wherein the second eye was not administered a photosensitizer, a protease, or light according to step b). In an exemplary embodiment, wherein

the results of step d) for the second eye comprise determining the average minimum vacuum needed to induce posterior vitreous detachment in the second eye, wherein the second eye was administered the protease, but was not administered a photosensitizer, or light according to step b).

III. Systems and/or Kits

[0048] In another aspect, the invention provides a system. In an exemplary embodiment, the system is useful for one of more of the reasons provided herein. In an exemplary embodiment, the system comprises: a photosensitizer and a light source to activate the photosensitizer. In an exemplary embodiment, the photosensitizer is as described herein and the light source is as described herein.

[0049] In another aspect, the invention provides a kit. In an exemplary embodiment, the kit is useful for one of more of the reasons provided herein. In an exemplary embodiment, the kit comprises: a photosensitizer, a light source to activate the photosensitizer, and instructions for use of the photosensitizer and the light source for one of more of the reasons provided herein. In an exemplary embodiment, the photosensitizer is as described herein and the light source is as described herein.

IV. Components of the Methods, Systems, and/or Kits

IV. a) Photosensitizers and Light Wavelengths

[0050] In an exemplary embodiment, the photosensitizer is selected from the group consisting of porphyrionoids, phthalocyanines, porphyrins, protoporphyrins, chlorins, bacteriochlorins, texaphyrins, porphycenes, corroles, verteporfin, halogenated fluoresceins, xanthenes, flavins, rhodamine, anthraquinones, phenothiazines, substituted cyanines, curcuminoids, and halogenated BODIPYs. In an exemplary embodiment, the photosensitizer is a phenothiazine. In an exemplary embodiment, the photosensitizer is riboflavin-5'-monophosphate and the wavelength of light ranges from 355 nm and 375 nm. In an exemplary embodiment, the photosensitizer is riboflavin-5'-monophosphate and the wavelength of light ranges from 445 nm and 465 nm. In an exemplary embodiment, the photosensitizer is fluorescein and the wavelength of light ranges from 490 nm and 510 nm. In an exemplary embodiment, the photosensitizer is eosin B and the wavelength of light ranges from 520 nm and 540 nm. In an exemplary embodiment, the photosensitizer is eosin Y and the wavelength of light ranges from 525 nm and 545 nm. In an

exemplary embodiment, the photosensitizer is erythrosin B and the wavelength of light ranges from 530 nm and 550 nm. In an exemplary embodiment, the photosensitizer is Rose Bengal and the wavelength of light ranges from 555 nm and 575 nm. In an exemplary embodiment, the photosensitizer is methylene blue and the wavelength of light ranges from 650 nm and 670 nm. In an exemplary embodiment, the photosensitizer is aluminum phthalocyanine chloride tetrasulfonate and the wavelength of light ranges from 680 nm and 700 nm. In an exemplary embodiment, the photosensitizer is verteporfin-visudyne and the wavelength of light ranges from 680 nm and 700 nm. In an exemplary embodiment, the photosensitizer is IR780 and the wavelength of light ranges from 770 nm and 790 nm. In an exemplary embodiment, the photosensitizer is indocyanine green and the wavelength of light ranges from 800 nm and 820 nm. In an exemplary embodiment, the photosensitizer is IR820 and the wavelength of light ranges from 810 nm and 830 nm.

[0051] In an exemplary embodiment, the photosensitizer is riboflavin-5'-monophosphate and the wavelength of light is about 365 nm. In an exemplary embodiment, the photosensitizer is riboflavin-5'-monophosphate and the wavelength of light is about 455 nm. In an exemplary embodiment, the photosensitizer is fluorescein and the wavelength of light is about 500 nm. In an exemplary embodiment, the photosensitizer is eosin B and the wavelength of light is about 530 nm. In an exemplary embodiment, the photosensitizer is eosin Y and the wavelength of light is about 535 nm. In an exemplary embodiment, the photosensitizer is erythrosin B and the wavelength of light is about 540 nm. In an exemplary embodiment, the photosensitizer is Rose Bengal and the wavelength of light is about 565 nm. In an exemplary embodiment, the photosensitizer is methylene blue and the wavelength of light is about 660 nm. In an exemplary embodiment, the photosensitizer is aluminum phthalocyanine chloride tetrasulfonate and the wavelength of light is about 690 nm. In an exemplary embodiment, the photosensitizer is verteporfin-visudyne and the wavelength of light is about 690 nm. In an exemplary embodiment, the photosensitizer is IR780 and the wavelength of light is about 780 nm. In an exemplary embodiment, the photosensitizer is indocyanine green and the wavelength of light is about 810 nm. In an exemplary embodiment, the photosensitizer is IR820 and the wavelength of light is about 820 nm.

[0052] In an exemplary embodiment, the photosensitizer is methylene blue and the wavelength of light ranges from 650 nm and 670 nm. In an exemplary embodiment, the photosensitizer is methylene blue and the wavelength of light is about 660 nm.

[0053] In an exemplary embodiment, the photosensitizer is porfimer sodium and the wavelength of light ranges from 622 nm and 642 nm. In an exemplary embodiment, the photosensitizer is meta-tetra(hydroxyphenyl)chlorin (m-THPC) and the wavelength of light ranges from 642 nm and 662 nm. In an exemplary embodiment, the photosensitizer is tin ethyl etiopurpurin and the wavelength of light ranges from 654 nm and 674 nm. In an exemplary embodiment, the photosensitizer is N-aspartyl chlorin e6 (NPe6) and the wavelength of light ranges from 654 nm and 674 nm. In an exemplary embodiment, the photosensitizer is 2-(1-Hexyloxyethyl)-2-devinylpyropheophorbide (HPPH) and the wavelength of light ranges from 655 nm and 675 nm. In an exemplary embodiment, the photosensitizer is palladium bacteriopheophorbide (WST09) and the wavelength of light ranges from 753 nm and 773 nm. In an exemplary embodiment, the photosensitizer is WST11 and the wavelength of light ranges from 740 nm and 760 nm. In an exemplary embodiment, the photosensitizer is motexafin lutetium (Lu-TeX) and the wavelength of light ranges from 722 nm and 742 nm. In an exemplary embodiment, the photosensitizer is silicon phthalocyanine and the wavelength of light ranges from 665 nm and 685 nm. In an exemplary embodiment, the photosensitizer is hypericin and the wavelength of light ranges from 580 nm and 600 nm. In an exemplary embodiment, the photosensitizer is toluidine blue and the wavelength of light ranges from 620 nm and 640 nm. In an exemplary embodiment, the photosensitizer is TH9402 and the wavelength of light ranges from 504 nm and 524 nm. In an exemplary embodiment, the photosensitizer is merocyanine 540 and the wavelength of light ranges from 546 nm and 566 nm. In an exemplary embodiment, the photosensitizer is curcumin and the wavelength of light ranges from 410 nm and 430 nm.

[0054] In an exemplary embodiment, the photosensitizer is porfimer sodium and the wavelength of light is about 632 nm. In an exemplary embodiment, the photosensitizer is meta-tetra(hydroxyphenyl)chlorin (m-THPC) and the wavelength of light is about 652 nm. In an exemplary embodiment, the photosensitizer is tin ethyl etiopurpurin and the wavelength of light is about 664 nm. In an exemplary embodiment, the photosensitizer is N-aspartyl chlorin e6 (NPe6) and the wavelength of light is about 664 nm. In an exemplary embodiment, the photosensitizer is 2-(1-Hexyloxyethyl)-2-devinylpyropheophorbide (HPPH) and the wavelength

of light is about 665 nm. In an exemplary embodiment, the photosensitizer is palladium bacteriophosphoribide (WST09) and the wavelength of light is about 763 nm. In an exemplary embodiment, the photosensitizer is WST11 and the wavelength of light is about 750 nm. In an exemplary embodiment, the photosensitizer is motexafin lutetium (Lu-TeX) and the wavelength of light is about 732 nm. In an exemplary embodiment, the photosensitizer is silicon phthalocyanine and the wavelength of light is about 675 nm. In an exemplary embodiment, the photosensitizer is hypericin and the wavelength of light is about 590 nm. In an exemplary embodiment, the photosensitizer is toluidine blue and the wavelength of light is about 630 nm. In an exemplary embodiment, the photosensitizer is TH9402 and the wavelength of light is about 514 nm. In an exemplary embodiment, the photosensitizer is merocyanine 540 and the wavelength of light is about 556 nm. In an exemplary embodiment, the photosensitizer is curcumin and the wavelength of light is about 420 nm.

[0055] The photosensitizers of the invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, a photosensitizer described herein may be radiolabeled with radioactive isotopes, such as for example deuterium (^2H), tritium (^3H), or carbon-14 (^{14}C). All isotopic variations of the compounds of the invention, whether radioactive or not, are intended to be encompassed within the scope of the invention. In an exemplary embodiment, a photosensitizer described herein is a deuterated photosensitizer. In an exemplary embodiment, methylene blue is deuterated methylene blue.

IV. b) Pharmaceutical Formulations containing the Photosensitizer

[0056] In an exemplary embodiment, the photosensitizer is administered to the mammal to provide an effective amount to the eye. The term "effective amount" of a photosensitizer described herein refers to a nontoxic but sufficient amount of the photosensitizer to provide the desired effect. The amount that is "effective" will vary from subject to subject, depending on the age and general condition of the individual, and the appropriate "effective" amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation. In an exemplary embodiment, the photosensitizer is administered to the mammal in an amount of from about 0.05 cc and about 10 cc. In an exemplary embodiment, the

photosensitizer is administered to the mammal in an amount of from about 0.1 mg/kg and about 10 mg/kg.

[0057] In an exemplary embodiment, the photosensitizer is part of a pharmaceutical formulation. In an exemplary embodiment, the pharmaceutical formulation comprises a photosensitizer and a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" refers to any formulation or carrier medium that provides the appropriate delivery of an effective amount of the photosensitizer described herein, does not interfere with the effectiveness of the biological activity of the photosensitizer, and that is sufficiently non-toxic to the mammal. Representative carriers include water (such as distilled water or deionized water), saline solution, Balance Salt Solution, and the like.

[0058] The pharmaceutically acceptable carrier of the invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, a pharmaceutically acceptable carrier described herein may be radiolabeled with radioactive isotopes, such as for example deuterium (^2H), tritium (^3H), or carbon-14 (^{14}C). All isotopic variations of the pharmaceutically acceptable carriers of the invention, whether radioactive or not, are intended to be encompassed within the scope of the invention. In an exemplary embodiment, a pharmaceutically acceptable carrier described herein is a deuterated pharmaceutically acceptable carrier. In an exemplary embodiment, the pharmaceutically acceptable carrier is deuterated water or a deuterated saline solution. Additional information concerning carriers can be found in *Remington: The Science and Practice of Pharmacy*, 23rd Ed., Academic Press (2020) which is incorporated herein by reference.

IV. c) Routes of Photosensitizer Administration

[0059] In an exemplary embodiment, the administering occurs through intravitreal, perbulbar, subtenons, oral, or intravenous administration of the photosensitizer to the mammal. In an exemplary embodiment, when the administering occurs through intravitreal administering, the amount of photosensitizer administered to the mammal ranges from about 0.05 cc and about 0.15 cc. In an exemplary embodiment, when the administering occurs through perbulbar administering, the amount of photosensitizer administered to the mammal ranges from about 0.1 cc and about 10 cc. In an exemplary embodiment, when the administering occurs through subtenons administering, the amount of photosensitizer administered to the mammal ranges from

about 0.1 cc and about 5 cc. In an exemplary embodiment, when the administering occurs through oral administering, the amount of photosensitizer administered to the mammal ranges from about 0.1 mg/kg and about 10 mg/kg. In an exemplary embodiment, when the administering occurs through intravenous administering, the amount of photosensitizer administered to the mammal ranges from about 0.1 mg/kg and about 10 mg/kg.

[0060] In an exemplary embodiment, when the administering occurs through intravitreal administering, the time from the administering and the irradiating ranges from about 1 minute and about 60 minutes. In an exemplary embodiment, when the administering occurs through peribulbar administering, the time from the administering and the irradiating ranges from about 1 minute and about 280 minutes. In an exemplary embodiment, when the administering occurs through subtenons administering, the time from the administering and the irradiating ranges from about 1 minute and about 180 minutes. In an exemplary embodiment, when the administering occurs through oral administering, the time from the administering and the irradiating ranges from about 1 minute and about 48 hours. In an exemplary embodiment, when the administering occurs through intravenous administering, the time from the administering and the irradiating ranges from about 1 minute and about 48 hours.

IV. d) Routes of Light Administration

[0061] In an exemplary embodiment, the irradiating occurs through methods such as transpupillary administration, intraocular administration, or transscleral administration. In an exemplary embodiment, the irradiating time ranges from about 1 minute and about 240 minutes. In an exemplary embodiment, the irradiating time ranges from about 30 minutes and about 240 minutes. In an exemplary embodiment, the irradiating time ranges from about 45 minutes and about 240 minutes. In an exemplary embodiment, the irradiating time ranges from about 60 minutes and about 240 minutes. In an exemplary embodiment, the irradiating time ranges from about 30 minutes and about 180 minutes. In an exemplary embodiment, the irradiating time ranges from about 45 minutes and about 180 minutes. In an exemplary embodiment, the irradiating time ranges from about 60 minutes and about 180 minutes. In an exemplary embodiment, the irradiating time ranges from about 60 minutes and about 90 minutes. In an exemplary embodiment, the irradiating time ranges from about 30 minutes and about 90 minutes. In an exemplary embodiment, the irradiating time ranges from about 45 minutes and about 90

minutes. In an exemplary embodiment, the irradiating time ranges from about 45 minutes and about 75 minutes. In an exemplary embodiment, the irradiating time ranges from about 55 minutes and about 75 minutes. In an exemplary embodiment, the irradiating time ranges from about 60 minutes and about 90 minutes. In an exemplary embodiment, the irradiating time ranges from about 25 minutes and about 95 minutes. In an exemplary embodiment, the irradiating time ranges from about 30 seconds to about 1,000 minutes. In an exemplary embodiment, the irradiating time ranges from about 30 seconds to about 60 minutes. In an exemplary embodiment, the irradiating time ranges from about 30 seconds to about 30 minutes. In an exemplary embodiment, the irradiating time ranges from about 30 seconds to about 20 minutes. In an exemplary embodiment, the irradiating time ranges from about 30 seconds to about 10 minutes. In an exemplary embodiment, the irradiating time ranges from about 5 minutes to about 45 minutes. In an exemplary embodiment, the irradiating time ranges from about 5 minutes to about 25 minutes. In an exemplary embodiment, the irradiating time ranges from about 3 minutes to about 13 minutes. In an exemplary embodiment, the irradiating time ranges from about 10 minutes to about 25 minutes. In an exemplary embodiment, the irradiating time ranges from about 15 minutes to about 45 minutes.

[0062] In an exemplary embodiment, the irradiating occurs through transpupillary administration. In an exemplary embodiment, when the irradiating occurs through transpupillary administration, the irradiating time ranges from about 1 minute and about 180 minutes, or from about 30 seconds to about 1,000 minutes, or from about 30 seconds to about 60 minutes, or from about 30 seconds to about 30 minutes, or from about 30 seconds to about 20 minutes, or from about 30 seconds to about 10 minutes, or from about 5 minutes to about 45 minutes, or from about 5 minutes to about 25 minutes, or from about 3 minutes to about 13 minutes, or from about 10 minutes to about 25 minutes, or from about 15 minutes to about 45 minutes. In an exemplary embodiment, when the irradiating occurs through transscleral administration, the irradiating time ranges from about 25 minutes and about 35 minutes. In an exemplary embodiment, the irradiating occurs through transscleral administration. In an exemplary embodiment, when the irradiating occurs through transscleral administration, the irradiating time ranges from about 1 minute and about 180 minutes. In an exemplary embodiment, the irradiating occurs through intraocular administration. In an exemplary embodiment, when the irradiating occurs through intraocular administration, the irradiating time ranges from about 1 minute and about 60 minutes.

In an exemplary embodiment, when the irradiating occurs through transscleral administration, the irradiating time ranges from about 25 minutes and about 35 minutes.

IV. e) Light Source

[0063] In an exemplary embodiment, the light source may depend on the route of light administration. In an exemplary embodiment, the light source is external to the eye. In an exemplary embodiment, the light source is internal to the eye. In an exemplary embodiment, when the irradiating is by transpupillary administration, the light source is a slit lamp delivery system. In an exemplary embodiment, when the irradiating is by transpupillary administration, the light source is an indirect ophthalmoscope delivery system. In an exemplary embodiment, when the irradiating is by transpupillary administration, the light source is LED. In an exemplary embodiment, when the irradiating is by transpupillary administration, the light source is a laser. In an exemplary embodiment, when the irradiating is by transpupillary administration, the light source involves multi-photon irradiation. In an exemplary embodiment, when the irradiating is by transpupillary administration, the light source involves two photon irradiation. In an exemplary embodiment, when the irradiating is by transscleral administration, the light source is a hand-held scleral probe. In an exemplary embodiment, the light source has an irradiance of from about 1 and about 1000 mW/cm². In an exemplary embodiment, the irradiance is sufficient to effect crosslinking at the vitreoretinal interface without significantly damaging the underlying retinal tissue.

[0064] Irradiation, such as by single photon excitation, two photon excitation, or multi-photon excitation, for example, is applied to the selected region of the vitreoretinal interface (VRI), thereby increasing the adhesion and/or the attachment (such as covalent attachment) of the vitreous to the retina.

[0065] A skilled artisan recognizes that the choice of photosensitizer dictates the type of light source employed, and that different photosensitizers are active at different wavelengths and with different efficiencies. In particular, the spatial resolution with which the photosensitizer can be excited is dependent on whether the photosensitizer is excited *via* single-photon or multi-photon excitation. The photosensitizers may be water soluble, inhibited by oxygen, and preferably biocompatible. Diffusion of the photosensitizer into the vitreous is governed by its size, and its hydrophilic and/or hydrophobic interactions with the vitreous. Desired diffusion rates should be

fast in order to minimize time from administration and irradiation. In an exemplary embodiment, the radiant exposure needed for an adhesion between vitreous and retina described herein ranges from about 0.01 J/cm² and about 60 J/cm² for a photosensitizer described herein. In an exemplary embodiment, the radiant exposure needed for covalent attachment between vitreous and retina described herein ranges from about 0.01 J/cm² and about 60 J/cm² for a photosensitizer described herein. In an exemplary embodiment, the radiant exposure needed for an adhesion between vitreous and retina described herein ranges from about 0.01 J/cm² and about 60 J/cm² for methylene blue, rose bengal, indocyanine green, riboflavin, or verteporfin. In an exemplary embodiment, the radiant exposure needed for covalent attachment between vitreous and retina described herein ranges from about 0.01 J/cm² and about 60 J/cm² for methylene blue, rose bengal, indocyanine green, riboflavin, or verteporfin. In an exemplary embodiment, the radiant exposure needed for an adhesion between vitreous and retina described herein ranges from about 0.01 J/cm² and about 60 J/cm² for methylene blue. In an exemplary embodiment, the radiant exposure for covalent attachment between vitreous and retina described herein ranges from about 0.01 J/cm² and about 60 J/cm² for methylene blue.

[0066] In certain embodiments, the light source may be defined as single photon excitation, two photon excitation, and multi-photon excitation. In particular aspects of the invention, imaging is used, for example optical coherence tomography (OCT), is employed, such as to characterize and target the VRI for irradiation and treatment (such as is described in U.S. Patent Application Serial No. 10/611,013, which is incorporated by reference herein in its entirety), for example. In an additional specific embodiment, light energy comes from any focused light source, including a laser source, for example. For single photon excitation, a skilled artisan recognizes that the light does not have to be focused and that a broad beam of light irradiating the tissue is sufficient. In an additional specific embodiment, selective regions for treatment are illuminated with light in a programmed pattern, by one of a number of techniques familiar to those skilled artisans, including, but not limited to programmed galvanometers or DLP micromirror arrays, for example. In another specific embodiment, light energy comes from a focused laser source, and the treatment area is controlled by one of a variety of techniques including, but not limited to, galvanometer steering optics.

[0067] OCT may be utilized for detection in the targeted tissues, such as detection of changes in the composition (such as scattering or labeling with a specific agent) or the organization of the vitreous.

[0068] The term "multi-photon excitation" as used herein refers to the application of light that may activate a photosensitizer through the near simultaneous absorption of more than one photon. This may be also stated as referring to the excitation of a photosensitizer by means of absorption or scattering of several photons simultaneously or near simultaneously. In a specific embodiment, the multi-photon excitation is of suitable intensity and wavelength to cause a photosensitizer to reach an activated state. Such multi-photon absorbance can take place by different processes, including those in which the photons activate the absorbing material through near simultaneous absorbance, and those in which the multiple photons are absorbed sequentially.

[0069] The term "single photon excitation" as used herein refers to the application of light that may activate a molecule through the absorption of a single photon. This may also be stated as the excitation of an atom or molecule by means of absorbing or scattering of a single photon.

[0070] The term "two photon excitation" as used herein refers to the application of light which may activate a molecule through the near simultaneous absorption of two photons. Stated in another way, it refers to excitation of an atom or molecule by means of absorption or scattering of two photons simultaneously or in close temporal proximity. Such two photon absorbance can take place by different processes, including those in which the photons activate the absorbing material through simultaneous or near-simultaneous absorbance, and those in which the two photons are absorbed sequentially.

IV. f) Locations of Vitreoretinal Interface (VRI) Selective Regions

[0071] In an exemplary embodiment, the selective region of the VRI comprises the fovea of the eye of the mammal. In an exemplary embodiment, the selective region of the VRI comprises the macula of the eye of the mammal. In an exemplary embodiment, the selective region of the VRI comprises the posterior pole of the eye of the mammal. In an exemplary embodiment, the selective region of the VRI comprises the bulk of the vitreous of the eye of the mammal. In an exemplary embodiment, the selective region of the VRI comprises the optic nerve of the eye of the mammal. In an exemplary embodiment, the selective region of the VRI comprises the region

surrounding the optic nerve of the eye of the mammal. In an exemplary embodiment, the selective region of the VRI comprises the region nasal to the optic nerve of the eye of the mammal. In an exemplary embodiment, the retina is the internal limiting membrane of the retina. In an exemplary embodiment, the retina is the ganglion cell layer of the retina.

[0072] In an exemplary embodiment, the selective region of the VRI in which the photosensitizer has accumulated, comprises the fovea of the eye of the mammal. In an exemplary embodiment, the selective region of the VRI in which the photosensitizer has accumulated comprises the macula of the eye of the mammal. In an exemplary embodiment, the selective region of the VRI in which the photosensitizer has accumulated comprises the posterior pole of the eye of the mammal. In an exemplary embodiment, the selective region of the VRI in which the photosensitizer has accumulated comprises the bulk of the vitreous of the eye of the mammal. In an exemplary embodiment, the selective region of the VRI in which the photosensitizer has accumulated comprises the optic nerve of the eye of the mammal. In an exemplary embodiment, the selective region of the VRI in which the photosensitizer has accumulated comprises the region around optic nerve of the eye of the mammal. In an exemplary embodiment, the selective region of the VRI in which the photosensitizer has accumulated comprises the region nasal to the optic nerve of the eye of the mammal. In an exemplary embodiment, the retina is the internal limiting membrane of the retina. In an exemplary embodiment, the retina is the ganglion cell layer of the retina.

[0073] In an exemplary embodiment, for slit lamp delivery of the irradiation, a contact lens is applied to the corneal surface using a coupling agent such as methylcellulose. This lens can enable the treating physician to focus the treatment beam on the selective region for VRI adhesion enhancement.

[0074] In an exemplary embodiment, selectively targeting the VRI in a particular retinal region is improved using retinal image-based eye tracking. In an exemplary embodiment, selective targeting of the VRI is done with a camera-based method. In an exemplary embodiment, selective targeting of the VRI is done using lasers via a scanning laser ophthalmoscope (SLO). Recent combination of SLO and adaptive optics (AO) have improved both the speed and resolution of retinal image-based tracking. AO can be combined with OCT as an alternative

method to track specific retinal regions. Such tracking systems would enable precise localization of VRI crosslinking.

IV. g) Mammal

[0075] In an exemplary embodiment, the mammal is a human, pig, cat, or dog. In an exemplary embodiment, the mammal is a pig. In an exemplary embodiment, the mammal is a human.

V. More specific embodiments

[0076] In an exemplary embodiment, the invention is a method of increasing adhesion between vitreous and retina in an eye of a human, comprising: intravenously administering from about 0.1 mg/kg and about 10 mg/kg of methylene blue to the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); irradiating the posterior pole of the VRI with light of a wavelength of from about 650 nm and about 670 nm through transpupillary administration for from about 25 minutes and about 95 minutes, thereby increasing adhesion between vitreous and retina in the eye of the human.

[0077] All publications and patent applications mentioned in this disclosure are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

[0078] No admission is made that any reference cited herein constitutes prior art. The discussion of the references states what their authors assert, and the Applicant reserves the right to challenge the accuracy and pertinence of the cited documents. It will be clearly understood that, although a number of information sources, including scientific journal articles, patent documents, and textbooks, are referred to herein; this reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art.

[0079] The discussion of the general methods given herein is intended for illustrative purposes only. Other alternative methods and alternatives will be apparent to those of skill in the art upon review of this disclosure, and are to be included within the spirit and purview of this application.

[0080] Additional embodiments are disclosed in further detail in the following examples, which are provided by way of illustration and are not in any way intended to limit the scope of this disclosure or the claims.

[0081] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0082] Although various features of the disclosure can be described in the context of a single embodiment, the features can also be provided separately or in any suitable combination. Conversely, although the present disclosure can be described herein in the context of separate embodiments for clarity, the present disclosure can also be implemented in a single embodiment.

EXAMPLES

[0083] The practice of the present invention will employ, unless otherwise indicated, conventional techniques of ophthalmology and photochemistry, which are well known to those skilled in the art. Additional information concerning the eye can be found in *Ryan's Retina*, 7th Ed., Elsevier (2022); *Gass' Atlas of Macular Diseases*, 5th Ed, Saunders (2012); and Michels, Wilkinson, & Rice, *Retinal Detachment*, Mosby Inc, (1990), each of which are incorporated herein by reference. Additional information concerning photochemistry can be found in Ormond et al., *Materials* 2013, 6, 817-840; Kamkaew et al., *Chem. Soc. Rev.*, 2013, 42, 77; Atchison et al., *Chem. Commun.*, 2017, 53, 2009; Swamy et al., *Coordination Chemistry Reviews*, 411 (2020) 213-233, each of which are incorporated herein by reference.

[0084] Additional embodiments are disclosed in further detail in the following examples, which are provided by way of illustration and are not in any way intended to limit the scope of this disclosure or the claims.

EXAMPLE 1

Photosensitizer crosslinking prevents formation of Posterior Vitreous Detachment (PVD) in *ex vivo* porcine model

[0085] **Methods:** Porcine eyes were used in the experiment. These experiments were conducted within 24 hrs of the death of the pig. As a negative control, 2U (in 0.1cc sterile water) of human plasmin was administered intravitreally to the porcine eye with 60 min incubation at 37°C. Plasmin was utilized as it induces PVD. As a positive control, 0.1cc 25% glutaraldehyde was administered intravitreally to the porcine eye with 90 min incubation at room temperature. Glutaraldehyde was utilized as it is a chemical crosslinking agent.

[0086] Experimental: A 1:100 solution of Methylene Blue 0.1cc was administered intravitreally to the porcine eye, followed by 15 min resting, followed by irradiation of the porcine eye with 660nm light for 30 min. Then, 2U (in 0.1cc sterile water) of human plasmin was administered intravitreally to the porcine eye with 60 min incubation at 37°C. Each porcine eye was then injected with blue food coloring to mask the presence of methylene blue. An ophthalmologist masked to treatment of each eye then dissected the porcine eyes and assessed vitreous attachment status.

[0087] Results:

<u>Type</u>	<u>Treatment</u>	<u>Total Number of Eyes</u>	<u>Number of Eyes with PVD</u>	<u>Number of Eyes without PVD</u>
Negative Control	Plasmin	6	5	1
Positive Control	Glutaraldehyde	4	0	4
Experimental	Methylene Blue/660nm + Plasmin	9	2	7

[0088] These results indicate that pre-treatment of the pig vitreoretinal interface with methylene blue and 660 nm irradiation can prevent PVD induction by intravitreal plasmin injection. This method could be adapted to other photo-initiators such as riboflavin/UV or riboflavin/2 photon; cosin Y/visible light, indocyanine green/NIR, rose bengal/visible light and others that are effective collagen crosslinkers.

EXAMPLE 2

Ex Vivo Vacuum Model

Methods

[0089] Vitreous adhesion to the retina was assessed using varying levels of vacuum with a 23-gauge vitrector (Constellation Vision System, Alcon, Fort Worth TX). This vitrector engaged the vitreous over the optic nerve and attempted to mechanically create a PVD. This was performed in an *ex vivo* porcine eye model. Control eyes with Balance Salt Solution (BSS) injection as well as those injected with increasing units of Plasmin were assessed for at which level of vacuum a PVD could be induced. 10 eyes were used for each concentration (units) of Plasmin injected.

Preparation and Injection of Plasmin

[0090] BSS (control) or 2U, 3U, or 5U of room-temperature Plasmin (Human, Sigma-Aldrich, St Louis MO) was injected in the porcine eyes 0.25mm from the edge of the optic nerve posteriorly (**FIG 1**). Eyes injected with BSS, 2U, 3U, or 5U of Plasmin were placed in 37°C water bath for 1 hour.

Inducing Posterior Vitreous Detachment

[0091] 23G cannulas were placed 4mm away from the corneal limbus. BSS Infusion was attached inferotemporally and infusion pressure was set to 30 mmHg. Wide field viewing was used to evaluate the retina - any eyes with pre-existing retinal detachment or PVD were excluded. Core and retrolental vitrectomy were performed to allow for movement in the mid-vitreous. A mixture of dilute triamcinolone and blue dye was instilled in the posterior vitreous around the optic nerve to enhance visualization of the vitreous. The vitrector was used to aspirate the peripapillary vitreous with increasing levels of vacuum (starting at 50 mmHg and increasing in 50 mmHg increments) to test the tensile strength of the vitreous attachment. Once PVD was induced, it was confirmed by repeat staining of the vitreous. If detachment occurred, the solution will aspirate within a few seconds.

Associating Vitrector Vacuum with Vitreous Fibril Tensile strength

[0092] To validate the relationship between vacuum and force the ability of the Alcon Constellation System to lift known masses on the lab bench was empirically tested. Due to the need to create a seal between the hand-piece opening and mass, a 23G soft tip was utilized for the experiment instead of the 23G vitrector. This relationship was anticipated by utilizing the two equations Force (F)= Mass (m) x Acceleration (a) and F= Pressure (p) x Area (A). Recognizing that the A will be the acceleration of gravity (g), the relationship between soft tip vacuum (pressure) and mass is $m = \frac{pA}{g}$. Therefore, there is a direct relationship between mass and pressure. The 23G soft-tip opening had a diameter of 0.6mm or 0.6×10^{-3} m. Therefore, the A was $2.82 \times 10^{-7} \text{m}^2$. Combining this with g, which was 9.8 m/s^2 , the equation of $m = 2.89 \times 10^{-8} \text{ ms}^2(\text{p})$ was generated. Adjusting for the units of pressure being mmHg and the masses in milligrams the equation was $m = 2.17 \times 10^{-16} \text{ ms}^2(\text{p})$.

Mass in Kg, pressure in pascal (n/m²), area in (m²), g (m/s²)

[0093] The Alcon Constellation System was set up with the 23G soft tip. Calibration masses (Taida, China) in milligrams were used as known masses. Vacuum settings were set to 50 mmHg without the cutter. Starting with the 50 mg weight, the vitrector opening was aligned with the surface of the mass and used to lift the mass. If the mass was not lifted, the vacuum setting was increased by 50 mmHg until the mass is lifted off the table. A positive response was set as lifting the mass off the table for at least 2 seconds. This process was repeated three times per mass.

Results

Vitrector vacuum directly relates to maximum possible lifted mass

[0094] Average of the vacuum necessary to lift standard masses was calculated. Data from this part of the study demonstrated a direct correlation between vitrector vacuum and the maximum mass that the system was able to lift (**FIG 2**). The data demonstrates a direct relationship between mass and the average minimum vacuum needed to lift the mass with high statistical significance indicated by the r-squared value of the relationship. The slope generated from the data was 1.68 ms^2 , which was higher than expected. This difference in slope and the value in the predictive equation may be due to manufacturing difference between the soft tips, the angle of the opening against the mass affecting the seal, and human variation. Since mass directly relates to force, this relationship also extends to the force generated by the adhesion of the vitreous. Stronger adhesion generates a higher effective mass and requires more tensile strength for separation. Therefore, the higher the vacuum needed for removal, the higher the tensile strength is between the vitreous and optic nerve head.

Increased Plasmin units injected was associated with lower vacuum needed to induce a PVD

[0095] Minimum vacuum needed to perform PVD near the optic disc was averaged and 95% confidence intervals (CI) and p-values were calculated per units of Plasmin (**FIG 3**). Statistical significance was set as p-values less than or equal to 0.05. Data demonstrated that increased Plasmin led to a decrease in the minimum vacuum necessary to induce a PVD. There is no statistically significant difference between 0U and 2U, with the average minimum vacuum needed to perform PVD being $395 \pm 28 \text{ mmHg}$ and $385 \pm 58 \text{ mmHg}$, respectively. There was a statistically significant difference ($p \leq 0.05$) between the minimum vacuum necessary to induce a PVD with 2U, 3U, and 5U of Plasmin, with the averages being $385 \pm 58 \text{ mmHg}$, $265 \pm 53 \text{ mmHg}$, and $145 \pm 28 \text{ mmHg}$, respectively.

[0096] Prior experimental methods for evaluating vitreous adhesion ex vivo relied upon dissection which necessarily affected the vitreous and its relationship to ocular structures. Aras et. al. In vivo generated autologous plasmin assisted vitrectomy in young patients. *Int J Retina Vitreous*. 2022 Jun 11;8(1):36 recognized this limitation and used the number of attempts required to achieve successful intraoperative separation of posterior hyaloid as more representative of the vitreous attachment *in situ*. A method is presented here to assess vitreous adhesion, more specifically the vacuum required to induce PVD, *in situ* using quantitative, clinically relevant techniques.

[0097] It is already well known that changes in concentration of Plasmin utilized can affect the quality of the detachment. Gandorfer et al. Ultrastructure of the vitreoretinal interface following plasmin assisted vitrectomy. *Br J Ophthalmol*. 2001 Jan;85(1):6-10. Our data demonstrates an expected dose-dependent response curve of intravitreal Plasmin on the average minimum vacuum needed to induce a PVD near the optic disc, strengthening the validity of our model.

[0098] Prior research in ex-vivo porcine eyes compared the effects of 1U and 2U of Plasmin on remaining vitreous attached to the ILM post vitrectomy. *Ibid*. They determined that 2U left no vitreous attached to the ILM confirmed by light, scanning, and transmission electron microscopy but 1U had remnants of Plasmin still attached post-treatment. This demonstrates that higher Plasmin concentrations lead to easier vitreous detachments. However, these studies typically either performed sclerectomies to perform imaging or had a binary output to determine if the vitreous detached or did not detach. Prior studies do not also specify where they are attempting to induce vitreous detachments either due to not specifying where the sclerectomy is specifically performed or performing their studies in patients, leading to complete vitrectomy being performed and tissue samples being collected for histology. Uemura et al. Effect of plasmin on laminin and fibronectin during plasmin-assisted vitrectomy. *Arch Ophthalmol*. 2005 Feb;123(2):209-13.

[0099] While the methodology described herein does not assess for vitreous remnants with micro-scale resolution that these other techniques offer, the clinical effects of PVD are sufficiently captured by this *in situ* assessment.

[0100] The data demonstrates statistically significant findings utilizing a novel methodology, however the techniques used within the experiment have their limitations. Porcine eyes had

varying quality, which was minimized by throwing out eyes with pre-existing globe ruptures, retinal detachments, and existing central PVDs. Unfortunately, prior central PVDs could only be assessed after prepping the eyes for experimentation because the trocars inserted for the vitrector, infusion, and light would leave multiple holes, leaving opportunities for the vitreous viscosity to be affected by environmental factors. To circumvent this issue, we utilized the fact that 5U of plasmin still required over 100mmHg of pressure to induce a PVD. Therefore, any eyes where a PVD was induced with 50mmHg was ruled to have a pre-existing PVD. A total of three eyes with pre-existing retinal detachment, seventeen eyes with pre-existing globe rupture, and twelve eyes with pre-existing vitreous detachment were used. One potential concern was if the eyes ruled with “pre-existing PVD” were outliers for higher doses of Plasmin. Of the eyes with pre-existing vitreous detachment, three were in eyes without any Plasmin and 3 were in eyes with 3U of Plasmin. While this ratio suggests a correlation between presence of Plasmin and pre-existing vitreous detachment, none of the eyes with 5U of Plasmin had pre-existing vitreous detachment. Therefore, the higher number of pre-existing vitreous detachments may be due to variation in eyes. Eyes with globe ruptures and retinal detachments were also excluded prior to injecting plasmin and testing for vitreous detachment, which could also skew the count of pre-existing vitreous detachments.

[0101] Given the tremendous impact vitreous status has on medical and surgical retinal disease it is important to develop models to assess the impact of various interventions on it. The current model offers significant benefits over prior work as it minimizes confounding manipulation and offers a quantitative assessment of vitreous adhesion.

EXAMPLE 3

Photosensitizer crosslinking prevents formation of Posterior Vitreous Detachment (PVD) in *ex vivo* vacuum model

Methods

[0102] Adhesion at the vitreoretinal interface was assessed using varying levels of vacuum with a 23-gauge vitrector (Constellation Vision System, Alcon, Fort Worth TX) to engage the vitreous over the optic nerve and attempt to mechanically create a PVD. This was performed in an *ex vivo* porcine eye model. Control eyes were administered with Balance Saline Solution injection (BSS), Glutaraldehyde, or 3U of Plasmin.

Preparation and Injection of Methylene Blue

[0103] Methylene Blue (1% USP grade, 50mL, Biopharm Inc., Hatfield, AR) was diluted to 1:100, 1:1,000, and 1:10,000 dilutions using sterile distilled water. All fat, muscle, and conjunctiva were dissected away from the posterior half of each eye. Eyes were injected with 0.3 mL of the solution utilizing the surgical microscope, wide-field lens, and Alcon Constellation light pipe to visualize placement of the methylene blue between the macula and optic nerve. Eyes sat for 30 minutes with the cornea up and optic nerve down to allow the majority of the solution time to collect in the back of the eye.

Activation of Methylene Blue with External Light Source

[0104] Eyes injected with Methylene Blue were placed cornea down on a surface. Flashlight (external light source) with wavelength of 660nm was placed above so that the light would shine only on the back of the eye (around 5.4 cm above the sclera at the posterior pole). The posterior half was covered with glycerin (to desiccate the sclera and/or improve light penetration). The eyes sat under the light for 30 minutes, 1 hour, and 1.5 hours.

Activation of Methylene Blue with Internal Light Source

[0105] Eyes injected with Methylene Blue were placed cornea up. A fiber optic cable (ThorLabs, Newton, NJ) (internal light source) was stripped 5cm to minimize the diameter of the hole. The cable was inserted so that the tip was pointing at the methylene blue pool in the eye around 1cm away from the edge of the pool. The intensity was set at 10%, 30%, 50%, and 70% of the maximum ($422.7 \pm 4.7 \text{ mW}$). The eye was irradiated for 30 minutes, 1 hour, and 1.5 hours.

Preparation and Injection of Glutaraldehyde

[0106] A 1% Solution was injected in the porcine eyes 0.25mm from the edge of the optic nerve. Eyes sat for 30 minutes with cornea up.

Preparation and Injection of Plasmin

[0107] 3U of room-temperature Plasmin (Human, Sigma-Aldrich, St Louis MO) was injected in the porcine eyes 0.25mm from the edge of the optic nerve posteriorly. Eyes were placed in 37°C water bath for 1 hour.

Inducing Posterior Vitreous Detachment

[0108] 23G cannulas were placed 4mm away from the corneal limbus. BSS Infusion was attached inferotemporally and infusion pressure was set to 30 mmHg. Wide field viewing was

used to evaluate the retina - any eyes with pre-existing retinal detachment or PVD were excluded. Core and retrolental vitrectomy were performed to allow for movement in the mid-vitreous. A mixture of dilute triamcinolone and blue dye was instilled in the posterior vitreous around the optic nerve to enhance visualization of the vitreous. The vitrector was used to aspirate the peripapillary vitreous with increasing levels of vacuum (starting at 50 mmHg and increasing in 50 mmHg increments) to test the tensile strength of the vitreous attachment. Once PVD was induced, it was confirmed by repeat staining of the vitreous. If it is detached, the solution will aspirate within a few seconds. All pressures per condition were averaged with the 95% confidence interval and p-values calculated. A p-value greater than 0.05 was set as statically significant.

Associating Methylene blue dilution with degree of light absorption

[0109] Methylene blue was diluted into 1:10, 1:100, 1:1,000, and 1:1,000 using sterile distilled water and made into 5, 10, 25mL quantities each. A powermeter (ThorLabs, Newton, NJ) was placed 5.4cm away from the end of the external 660nm flashlight. The power was measured three times. A standard 50mL beaker was placed on top of the receptive end of the power meter and the power was measured three times. The power of the light was then measured three times for each of the following conditions: 25mL water, 5mL of 1:10 dilution, 5mL of 1:100 dilution, 5mL of 1:1000 dilution, 5mL of 1:10000 dilution, 10mL of 1:10 dilution, 10mL of 1:100 dilution, 10mL of 1:1000 dilution, 10mL of 1:10000 dilution, 25mL of 1:10 dilution, 25mL of 1:100 dilution, 25mL of 1:1000 dilution, and 25mL of 1:10000 dilution. All powers per condition were averaged with the 95% confidence interval and p-values calculated. A p-value greater than 0.05 was set as statically significant.

Associating percentage of Maximum Intensity of the Internal 660nm light with Power

[0110] The fiberoptic cable utilized to irradiate the porcine eye internally was set to 0.1. The power meter was set 1cm away from the end of the cable. The power was measured three times. This process was repeated for 0.2, 0.5, and 1 setting. All powers per condition were averaged with the 95% confidence interval and p-values calculated. A p-value greater than 0.05 was set as statically significant.

Results/ Discussion

Minimum necessary concentration of Methylene Blue needed to Induce Crosslinking is 1:1000

[0111] Prior work performed by Dr. Christopher Marotta at Caltech determined that the minimum concentration needed to induce crosslinking in a modeled vitreous using type 4 collagen was 1:1,000 dilution.

[0112] A proof-of-concept experiment was performed at the beginning utilizing 1:100 and 1:1,000 dilutions. However, the outcome was binary due to the alternative method of testing ease of vitreous detachment by creating an eye cup. One surgeon used Weck-Cel spears to manipulate the vitreous and qualitatively determine ease of detachment (**FIG 4**). Data demonstrated that plasmin and glutaraldehyde were able to induce and prevent a PVD respectively. It also demonstrated that 1:1000 dilution may not be enough methylene blue to crosslink enough vitreous to retina consistently.

[0113] This experiment was extended by associating the degree of dilution and volume of fluid with the amount of light absorption (**FIG 5**). Too low concentrations allow for almost all light to penetrate through the liquid, letting the power meter measure near baseline levels of power from the light source. Data demonstrated that the average power at 5.4cm away from the flashlight was 16.5 ± 0.2 mW. With the beaker (glass) the average power increases to 42.6 ± 0.2 mW. This is most likely due to the bending of light at the not-flat bottom of the beaker, which acts like a convex lens funneling the light towards the center of the beaker where the receptive end of the power meter is located (**FIG 6**). The average power with the different volumes of water demonstrates the effect of larger volume of liquid on the transmission of light, with the average powers of 5, 10, and 25mL being 37.9 ± 0.2 , 35.9 ± 0.3 , and 29.4 ± 0.3 mW respectively. This trend holds true with the highest dilution of 1:10,000. The average powers at 5, 10, and 25mL are 27.6 ± 0.6 , 23.5 ± 0.4 , and 10.2 ± 0.2 mW respectively. The averages are lower than just water due to the very dilute methylene blue absorbing some of the light transmitting through, lowering the power measured. Dilutions of 1:10, 1:100, and 1:1000 demonstrate the ability to block the transmission of light through the solution expect for 5mL of 1:1000 at 3.0 ± 0.3 mW. All p-values demonstrates statically significant differences between the average powers measured. While this data is not exactly a replication of the porcine model, it does demonstrate the need to balance enough methylene blue to within the eye to crosslink enough of the vitreous to the retina while

not putting too much into the eye where the light is unable to transmit through the solution and crosslink the majority of the methylene blue injected into the eye.

Minimum necessary time under external 660 nm flashlight is One hour

[0114] Eyes were placed under the external light 5.4 cm away for 30 minutes (7 eyes), 1 hour (14 eyes), and 1.5 hours (7 eyes). The average pressure required to induce a PVD after 30 minutes was 421.4 ± 69.9 mmHg. Eyes under the light for 1 hour had an average pressure of 557.1 ± 123.8 mmHg. Eyes under the light for 1.5 hours had an average pressure of 543.2 ± 130.2 mmHg. Therefore there is a statistically significant difference between 30 minutes versus the other two times (p value 0.004) but no difference between 1 hour and 1.5 hours (p value 0.07). Therefore the minimum time necessary to induce a PVD is 1 hour.

Minimum necessary distance is 5.4cm with external 660nm flashlight

[0115] Eyes were placed at 8cm (8 eyes) and 5.4 cm (14 eyes) away from the external light source to evaluate the effect distance had on crosslinking effect. The average pressure required to induce a PVD 8 cm away was 381.3 ± 110.0 mmHg. Eyes 5.4cm away had an average pressure of 557.1 ± 123.8 mmHg. There was a statistically significant difference between the two (p-value 0.003). In the experimental set up, 5.4 cm away was close enough to allow the light from the flashlight to cover the most amount of posterior part of the eye with minimal stray light. Therefore, the maximum effect of the methylene blue was noticed at 5.4 cm away from the light source.

Internal Irradiation does not have an effect despite the increase in intensity

[0116] The power from the fiberoptic cable was measured at different intensities (**FIG 7**). The data demonstrates differences in average power measured with the lowest setting demonstrating a power of 12.4 ± 0.4 mW and the highest measuring 422.7 ± 4.7 mW. The p-values demonstrated statistically significant differences in average power measured. Therefore, there should be better irradiation with increased intensity.

[0117] However, the data from the average minimum pressure to induce a PVD demonstrates that the intensity of the light has no effect on the average minimum pressure to induce a PVD. The average pressure with methylene blue and plasmin with the internal 660nm light at 10% (5 eyes) was 360 ± 65.2 mmHg, 20% (4 eyes) was 375 ± 86.6 mmHg, and 50% (4 eyes) was 362.5 ± 47.9 mmHg. 100% was tested but not used due to the light burning the retina at that

intensity, and therefore, won't be used in in-vivo or clinical trials. The p-value, as expected, demonstrated no statistical significance between the intensities. However, the average pressure needed with the external light was 557.1 ± 123.8 mmHg, which is statistically significantly more than with the internal light (p value of 0.0005, 0.01, and 0.0003 for 10, 20, and 50% respectively). This suggested that the light is not activating the methylene blue to the same extent as the external light or that the light is unable to crosslink enough of the methylene blue due to the light shining at the methylene blue farthest away from the back of the eye first, leading to methylene blue blocking the light from irradiating the methylene blue closest to the vitreoretinal interface.

Inactivated Methylene Blue Leads to Similar Results as No Methylene Blue

[0118] Data comparing the effects of plasmin, methylene blue, the external light, and Glutaraldehyde on the average minimum pressure needed to induce a PVD was measured (**FIG 8**). The data demonstrates that injecting the methylene blue alone without additional photoactivation (10 eyes) has no effect on the average pressure as plasmin alone (10 eyes) has an average of 195.0 ± 65.2 mmHg and methylene blue and plasmin has an average of 215.0 ± 47.4 mmHg. The p- value was 0.37 which demonstrates no statically significant difference. Therefore the methylene blue alone has no effect on the vitreoretinal interface.

Irradiation alone does not account for the effect of Activated Methylene Blue

[0119] Data from the same figure also compared the effect of 660nm illumination on the vitreoretinal interface. Normal eyes only injected with BSS (10 eyes) had an average minimum pressure of 395.0 ± 22.4 mmHg and eyes with just plasmin (10 eyes) were 195.0 ± 65.2 mmHg. However the eyes with light and plasmin (10 eyes) had an average of 355.0 ± 36.9 mmHg. The suction force required to induce a PVD in the light with plasmin eyes was statistically significantly different than that of plasmin alone (p value of 1.8×10^{-7}) and control eyes (p value of 0.01). However, this remains significantly below the required pressure for eyes treated with both methylene blue and external light.

Crosslinking from Methylene Blue is almost as strong as Crosslinking from Glutaraldehyde

[0120] Data from the same figure also compared the effect of activated methylene blue to the glutaraldehyde, a known crosslinking agent. The average minimum pressure to induce a PVD in the activated methylene blue (14 eyes) was 557.1 ± 123.8 mmHg and glutaraldehyde (10 eyes) was

630±25.8 mmHg. While the standard deviation and 95% confidence interval bars overlap, the p-value was 0.04995 rounding up to 0.05. Therefore, there is a statistically significant difference between the effect of the two reagents, although slight. This indicates that the activated methylene blue increases adhesion nearly as much as the glutaraldehyde.

[0121] Notwithstanding the appended claims, the disclosure is also defined by the following clauses:

[0122] 1. A method of preventing an ocular condition through effecting targeted enhanced adhesion between cortical vitreous and retina in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region of the VRI with light of a wavelength by which crosslinking occurs between the cortical vitreous and the retina thereby preventing an ocular condition through effecting targeted enhanced between cortical vitreous and retina in the eye of the mammal.

[0123] 2. The method of clause 1, wherein the ocular condition is complete posterior vitreous detachment, retinal tear, rhegmatogenous retinal detachment, macular hole, epiretinal membrane, or a vitreous floater.

[0124] 3. The method of clause 1, wherein when the ocular condition is posterior vitreous detachment, the selective region of the VRI comprises an area nasal to the optic nerve; when the ocular condition is retinal tear, the selective region of the VRI comprises an area nasal to the optic nerve; when the ocular condition is rhegmatogenous retinal detachment, the selective region of the VRI comprises an area nasal to the optic nerve; when the ocular condition is macular hole, the selective region of the VRI comprises the macula or area around the macula; when the ocular condition is epiretinal membrane, the selective region of the VRI comprises the macula or area around the macula; or when the ocular condition is a vitreous opacity, the selective region of the VRI comprises an area nasal to the optic nerve or around the optic nerve.

[0125] 4. A method of increasing adhesion between vitreous and retina in an eye of a mammal, comprising: administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and irradiating a selective region

of the VRI with light of a wavelength by which crosslinking occurs between the vitreous and the retina thereby increasing adhesion between vitreous and retina in the eye of the mammal.

[0126] 5. The method of a preceding clause, wherein the irradiating is with light of a wavelength by which the photosensitizer induces crosslinking between the vitreous and the retina.

[0127] 6. The method of a preceding clause, wherein the administering occurs through intravitreal, perbulbar, subtenons, oral, or intravenous administration of the photosensitizer to the mammal.

[0128] 7. The method of a preceding clause, wherein when the administering occurs through intravitreal administering, the amount of photosensitizer ranges from about 0.05 cc and about 0.15 cc; through perbulbar administering, the amount of photosensitizer ranges from about 0.1 cc and about 10 cc; through subtenons administering, the amount of photosensitizer ranges from about 0.1 cc and about 5 cc; through oral administering, the amount of photosensitizer ranges from about 0.1 mg/kg and about 10 mg/kg; or through intravenous administering, the amount of photosensitizer ranges from about 0.1 mg/kg and about 10 mg/kg.

[0129] 8. The method of a preceding clause, wherein when the administering occurs through intravitreal administering, the time from the administering and the irradiating ranges from about 1 minute and about 60 minutes; through perbulbar administering, the time from the administering and the irradiating ranges from about 1 minute and about 280 minutes; through subtenons administering, the time from the administering and the irradiating ranges from about 1 minute and about 180 minutes; through oral administering, the time between the administering and the irradiating ranges from about 1 minute and about 48 hours; or through intravenous administering, the time from the administering and the irradiating ranges from about 1 minute and about 48 hours.

[0130] 9. The method of a preceding clause, wherein the irradiating occurs through transscleral administration, transpupillary administration, or intraocular administration of the light.

[0131] 10. The method of a preceding clause, wherein when the irradiating occurs through transscleral administration, the irradiating time ranges from about 1 minute and about 180 minutes; through transpupillary administration, the irradiating time ranges from about 1 minute

and about 180 minutes; or through intraocular administration, the irradiating time ranges from about 1 minute and about 60 minutes.

[0132] 11. The method of clause 10, wherein when the irradiating occurs through transscleral administration, the irradiating time ranges from about 25 minutes and about 35 minutes.

[0133] 12. The method of a preceding clause, wherein the selective region of the VRI comprises the fovea of the eye of the mammal.

[0134] 13. The method of a preceding clause, wherein the selective region of the VRI comprises the macula of the eye of the mammal.

[0135] 14. The method of a preceding clause, wherein the selective region of the VRI comprises the posterior pole of the eye of the mammal.

[0136] 15. The method of a preceding clause, wherein the selective region of the VRI comprises the bulk of the vitreous of the eye of the mammal.

[0137] 16. The method of a preceding clause, wherein the selective region of the VRI comprises the optic nerve, or the region nasal to the optic nerve, of the eye of the mammal.

[0138] 17. The method of a preceding clause, wherein the retina is the internal limiting membrane of the retina.

[0139] 18. The method of a preceding clause, wherein the retina is the ganglion cell layer of the retina.

[0140] 19. The method of a preceding clause, wherein the photosensitizer is selected from the group consisting of porphyrionoids, phthalocyanines, porphyrins, protoporphyrins, chlorins, bacteriochlorins, texaphyrins, porphycenes, corroles, verteporfins, halogenated fluoresceins, xanthenes, flavins, rhodamine, anthraquinones, phenothiazines, substituted cyanines, curcuminoids, and halogenated BODIPYs.

[0141] 20. The method of a preceding clause, wherein the photosensitizer is a phenothiazine.

[0142] 21. The method of a preceding clause, wherein the photosensitizer is riboflavin-5'-monophosphate and the wavelength of light ranges from 355 nm and 375 nm, the photosensitizer is riboflavin-5'-monophosphate and the wavelength of light ranges from 445 nm and 465 nm, the photosensitizer is fluorescein and the wavelength of light ranges from 490 nm and 510 nm, the

photosensitizer is eosin B and the wavelength of light ranges from 520 nm and 540 nm, the photosensitizer is eosin Y and the wavelength of light ranges from 525 nm and 545 nm, the photosensitizer is erythrosin B and the wavelength of light ranges from 530 nm and 550 nm, the photosensitizer is Rose Bengal and the wavelength of light ranges from 555 nm and 575 nm, the photosensitizer is methylene blue and the wavelength of light ranges from 650 nm and 670 nm, the photosensitizer is aluminum phthalocyanine chloride tetrasulfonate and the wavelength of light ranges from 680 nm and 700 nm, the photosensitizer is verteporfin-visudyne and the wavelength of light ranges from 680 nm and 700 nm, the photosensitizer is IR780 and the wavelength of light ranges from 770 nm and 790 nm, the photosensitizer is indocyanine green and the wavelength of light ranges from 800 nm and 820 nm, and the photosensitizer is IR820 and the wavelength of light ranges from 810 nm and 830 nm.

[0143] 22. The method of a preceding clause, wherein the photosensitizer is riboflavin-5'-monophosphate and the wavelength of light is about 365 nm, the photosensitizer is riboflavin-5'-monophosphate and the wavelength of light is about 455 nm, the photosensitizer is fluorescein and the wavelength of light is about 500 nm, the photosensitizer is eosin B and the wavelength of light is about 530 nm, the photosensitizer is eosin Y and the wavelength of light is about 535 nm, the photosensitizer is erythrosin B and the wavelength of light is about 540 nm, the photosensitizer is Rose Bengal and the wavelength of light is about 565 nm, the photosensitizer is methylene blue and the wavelength of light is about 660 nm, the photosensitizer is aluminum phthalocyanine chloride tetrasulfonate and the wavelength of light is about 690 nm, the photosensitizer is verteporfin-visudyne and the wavelength of light is about 690 nm, the photosensitizer is IR780 and the wavelength of light is about 780 nm, the photosensitizer is indocyanine green and the wavelength of light is about 810 nm, and the photosensitizer is IR820 and the wavelength of light is about 820 nm.

[0144] 23. The method of a preceding clause, wherein the photosensitizer is methylene blue and the wavelength of light ranges from 650 nm and 670 nm.

[0145] 24. The method of a preceding clause, wherein the photosensitizer is methylene blue and the wavelength of light is about 660 nm.

[0146] 25. The method of a preceding clause, wherein the mammal is a human or a pig.

[0147] 26. A method of increasing adhesion between vitreous and retina in an eye of a human, comprising: intravenously administering from about 0.1 mg/kg and about 10 mg/kg of methylene blue to the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); irradiating the posterior pole of the VRI with light of a wavelength of about 660 nm through transpupillary administration from about 25 minutes and about 95 minutes thereby increasing adhesion between vitreous and retina in the eye of the human.

[0148] In at least some of the previously described embodiments, one or more elements used in an embodiment can interchangeably be used in another embodiment unless such a replacement is not technically feasible. It will be appreciated by those skilled in the art that various other omissions, additions and modifications may be made to the methods and structures described above without departing from the scope of the claimed subject matter. All such modifications and changes are intended to fall within the scope of the subject matter, as defined by the appended claims.

[0149] It will be understood by those within the art that, in general, terms used herein, and especially in the appended claims (e.g., bodies of the appended claims) are generally intended as “open” terms (e.g., the term “including” should be interpreted as “including but not limited to,” the term “having” should be interpreted as “having at least,” the term “includes” should be interpreted as “includes but is not limited to,” etc.). It will be further understood by those within the art that if a specific number of an introduced claim recitation is intended, such an intent will be explicitly recited in the claim, and in the absence of such recitation no such intent is present. For example, as an aid to understanding, the following appended claims may contain usage of the introductory phrases “at least one” and “one or more” to introduce claim recitations. However, the use of such phrases should not be construed to imply that the introduction of a claim recitation by the indefinite articles “a” or “an” limits any particular claim containing such introduced claim recitation to embodiments containing only one such recitation, even when the same claim includes the introductory phrases “one or more” or “at least one” and indefinite articles such as “a” or “an” (e.g., “a” and/or “an” should be interpreted to mean “at least one” or “one or more”); the same holds true for the use of definite articles used to introduce claim recitations. In addition, even if a specific number of an introduced claim recitation is explicitly recited, those skilled in the art will recognize that such recitation should be interpreted to mean at least the recited number (e.g., the bare recitation of “two recitations,” without other modifiers,

means at least two recitations, or two or more recitations). Furthermore, in those instances where a convention analogous to “at least one of A, B, and C, etc.” is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (e.g., “a system having at least one of A, B, and C” would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). In those instances where a convention analogous to “at least one of A, B, or C, etc.” is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (e.g., “a system having at least one of A, B, or C” would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). It will be further understood by those within the art that virtually any disjunctive word and/or phrase presenting two or more alternative terms, whether in the description, claims, or drawings, should be understood to contemplate the possibilities of including one of the terms, either of the terms, or both terms. For example, the phrase “A or B” will be understood to include the possibilities of “A” or “B” or “A and B.”

[0150] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[0151] As will be understood by one skilled in the art, for any and all purposes, such as in terms of providing a written description, all ranges disclosed herein also encompass any and all possible sub-ranges and combinations of sub-ranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, etc. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, etc. As will also be understood by one skilled in the art all language such as “up to,” “at least,” “greater than,” “less than,” and the like include the number recited and refer to ranges which can be subsequently broken down into sub-ranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member. Thus, for example, a group having 1-3 articles refers to groups having 1, 2, or 3 articles. Similarly, a group having 1-5 articles refers to groups having 1, 2, 3, 4, or 5 articles, and so forth.

[0152] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

[0153] Accordingly, the preceding merely illustrates the principles of the invention. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the invention and are included within its spirit and scope. Furthermore, all examples and conditional language recited herein are principally intended to aid the reader in understanding the principles of the invention and the concepts contributed by the inventors to furthering the art, and are to be construed as being without limitation to such specifically recited examples and conditions. Moreover, all statements herein reciting principles, aspects, and embodiments of the invention as well as specific examples thereof, are intended to encompass both structural and functional equivalents thereof. Additionally, it is intended that such equivalents include both currently known equivalents and equivalents developed in the future, i.e., any elements developed that perform the same function, regardless of structure. Moreover, nothing disclosed herein is intended to be dedicated to the public regardless of whether such disclosure is explicitly recited in the claims.

[0154] The scope of the present invention, therefore, is not intended to be limited to the exemplary embodiments shown and described herein. Rather, the scope and spirit of present invention is embodied by the appended claims. In the claims, 35 U.S.C. §112(f) or 35 U.S.C. §112(6) is expressly defined as being invoked for a limitation in the claim only when the exact phrase "means for" or the exact phrase "step for" is recited at the beginning of such limitation in the claim; if such exact phrase is not used in a limitation in the claim, then 35 U.S.C. § 112 (f) or 35 U.S.C. §112(6) is not invoked.

WHAT IS CLAIMED IS:

1. A method of preventing an ocular condition through effecting targeted enhanced adhesion between cortical vitreous and retina in an eye of a mammal, comprising:
administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and
irradiating a selective region of the VRI with light of a wavelength by which crosslinking occurs between the cortical vitreous and the retina
thereby preventing an ocular condition through effecting targeted enhanced between cortical vitreous and retina in the eye of the mammal.
2. The method of claim 1, wherein the ocular condition is complete posterior vitreous detachment, retinal tear, rhegmatogenous retinal detachment, macular hole, epiretinal membrane, or a vitreous floater.
3. The method of claim 1, wherein
when the ocular condition is posterior vitreous detachment, the selective region of the VRI comprises an area nasal to the optic nerve;
when the ocular condition is retinal tear, the selective region of the VRI comprises an area nasal to the optic nerve;
when the ocular condition is rhegmatogenous retinal detachment, the selective region of the VRI comprises an area nasal to the optic nerve;
when the ocular condition is macular hole, the selective region of the VRI comprises the macula or area around the macula;
when the ocular condition is epiretinal membrane, the selective region of the VRI comprises the macula or area around the macula; or
when the ocular condition is a vitreous opacity, the selective region of the VRI comprises an area nasal to the optic nerve or around the optic nerve.
4. A method of increasing adhesion between vitreous and retina in an eye of a mammal, comprising:
administering a photosensitizer to the eye of the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI); and

irradiating a selective region of the VRI with light of a wavelength by which crosslinking occurs between the vitreous and the retina thereby increasing adhesion between vitreous and retina in the eye of the mammal.

5. The method of claim 4, wherein the irradiating is with light of a wavelength by which the photosensitizer induces crosslinking between the vitreous and the retina.

6. The method of claim 4 or 5, wherein the administering occurs through intravitreal, perbulbar, subtenons, oral, or intravenous administration of the photosensitizer to the mammal.

7. The method of any one of claims 4-6, wherein when the administering occurs through intravitreal administering, the amount of photosensitizer ranges from about 0.05 cc and about 0.15 cc;
through perbulbar administering, the amount of photosensitizer ranges from about 0.1 cc and about 10 cc;
through subtenons administering, the amount of photosensitizer ranges from about 0.1 cc and about 5 cc;
through oral administering, the amount of photosensitizer ranges from about 0.1 mg/kg and about 10 mg/kg; or
through intravenous administering, the amount of photosensitizer ranges from about 0.1 mg/kg and about 10 mg/kg.

8. The method of any one of claims 4-7, wherein when the administering occurs through intravitreal administering, the time from the administering and the irradiating ranges from about 1 minute and about 60 minutes;
through perbulbar administering, the time from the administering and the irradiating ranges from about 1 minute and about 280 minutes;
through subtenons administering, the time from the administering and the irradiating ranges from about 1 minute and about 180 minutes;
through oral administering, the time from the administering and the irradiating ranges from about 1 minute and about 48 hours; or
through intravenous administering, the time from the administering and the irradiating ranges from about 1 minute and about 48 hours.

9. The method of any one of claims 4-8, wherein the irradiating occurs through transscleral administration, transpupillary administration, or intraocular administration of the light.
10. The method of any one of claims 4-9, wherein when the irradiating occurs through transscleral administration, the irradiating time ranges from about 1 minute and about 180 minutes;
through transpupillary administration, the irradiating time ranges from about 1 minute and about 180 minutes; or
through intraocular administration, the irradiating time ranges from about 1 minute and about 60 minutes.
11. The method of claim 10, wherein when the irradiating occurs through transscleral administration, the irradiating time ranges from about 25 minutes and about 35 minutes.
12. The method of any one of claims 4-11, wherein the selective region of the VRI comprises the fovea of the eye of the mammal.
13. The method of any one of claims 4-11, wherein the selective region of the VRI comprises the macula of the eye of the mammal.
14. The method of any one of claims 4-11, wherein the selective region of the VRI comprises the posterior pole of the eye of the mammal.
15. The method of any one of claims 4-11, wherein the selective region of the VRI comprises the bulk of the vitreous of the eye of the mammal.
16. The method of any one of claims 4-11, wherein the selective region of the VRI comprises the optic nerve, or the region nasal to the optic nerve, of the eye of the mammal.
17. The method of any one of claims 4-11, wherein the retina is the internal limiting membrane of the retina.
18. The method of any one of claims 4-11, wherein the retina is the ganglion cell layer of the retina.

- 19.** The method of any one of claims **4-18**, wherein the photosensitizer is selected from the group consisting of porphyrionoids, phthalocyanines, porphyrins, protoporphyrins, chlorins, bacteriochlorins, texaphyrins, porphycenes, corroles, verteporfin, halogenated fluoresceins, xanthenes, flavins, rhodamine, anthraquinones, phenothiazines, substituted cyanines, curcuminoids, and halogenated BODIPYs.
- 20.** The method of any one of claims **4-18**, wherein the photosensitizer is a phenothiazine.
- 21.** The method of any one of claims **4-18**, wherein the photosensitizer is riboflavin-5'-monophosphate and the wavelength of light ranges from 355 nm and 375 nm, the photosensitizer is riboflavin-5'-monophosphate and the wavelength of light ranges from 445 nm and 465 nm, the photosensitizer is fluorescein and the wavelength of light ranges from 490 nm and 510 nm, the photosensitizer is eosin B and the wavelength of light ranges from 520 nm and 540 nm, the photosensitizer is eosin Y and the wavelength of light ranges from 525 nm and 545 nm, the photosensitizer is erythrosin B and the wavelength of light ranges from 530 nm and 550 nm, the photosensitizer is Rose Bengal and the wavelength of light ranges from 555 nm and 575 nm, the photosensitizer is methylene blue and the wavelength of light ranges from 650 nm and 670 nm, the photosensitizer is aluminum phthalocyanine chloride tetrasulfonate and the wavelength of light ranges from 680 nm and 700 nm, the photosensitizer is verteporfin-visudyne and the wavelength of light ranges from 680 nm and 700 nm, the photosensitizer is IR780 and the wavelength of light ranges from 770 nm and 790 nm, the photosensitizer is indocyanine green and the wavelength of light ranges from 800 nm and 820 nm, and the photosensitizer is IR820 and the wavelength of light ranges from 810 nm and 830 nm.
- 22.** The method of any one of claims **4-18**, wherein the photosensitizer is riboflavin-5'-monophosphate and the wavelength of light is about 365 nm, the photosensitizer is riboflavin-5'-monophosphate and the wavelength of light is about 455 nm, the photosensitizer is fluorescein and the wavelength of light is about 500 nm, the photosensitizer is eosin B and the wavelength of light is about 530 nm, the photosensitizer is eosin Y and the wavelength of light is about 535 nm, the photosensitizer is erythrosin B and the wavelength of light is about 540 nm, the photosensitizer is Rose Bengal and the wavelength of light is about 565 nm, the photosensitizer is methylene blue and the wavelength of light is about 660 nm, the photosensitizer is aluminum

phthalocyanine chloride tetrasulfonate and the wavelength of light is about 690 nm, the photosensitizer is verteporfin-visudyne and the wavelength of light is about 690 nm, the photosensitizer is IR780 and the wavelength of light is about 780 nm, the photosensitizer is indocyanine green and the wavelength of light is about 810 nm, and the photosensitizer is IR820 and the wavelength of light is about 820 nm.

23. The method of any one of claims **4-18**, wherein the photosensitizer is methylene blue and the wavelength of light ranges from 650 nm and 670 nm.

24. The method of any one of claims **4-18**, wherein the photosensitizer is methylene blue and the wavelength of light is about 660 nm.

25. The method of any one of claims **4-24**, wherein the mammal is a human or a pig.

26. A method of increasing adhesion between vitreous and retina in an eye of a human, comprising:
intravenously administering from about 0.1 mg/kg and about 10 mg/kg of methylene blue to the mammal, wherein the photosensitizer accumulates at the vitreoretinal interface (VRI);
irradiating the posterior pole of the VRI with light of a wavelength of about 660 nm through transpupillary administration for between about 25 minutes and about 95 minutes
thereby increasing adhesion between vitreous and retina in the eye of the human.