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(54) **INTRAOCULAR PRESSURE SENSING MATERIAL, DEVICES, AND USES THEREOF**

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(57) **ABSTRACT**

Described herein are eye implants that can include a pressure-responsive material that can be capable of changing color in response to pressure exerted on it. Also described here are methods of implanting and using the eye implants described herein to monitor intraocular pressure in a subject. The pressure-responsive material can be used to diagnose and monitor human or animal subjects.

INTRAOCULAR PRESSURE SENSING MATERIAL, DEVICES, AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application is a continuation of U.S. patent application Ser. No. 17/051,051, having the title "INTRAOCULAR PRESSURE SENSING MATERIAL, DEVICES, AND USES THEREOF", filed on Oct. 27, 2020, which is the 35 U.S.C. § 371 national stage application of PCT Application No. PCT/US2019/038193, filed Jun. 20, 2019, where the PCT claims priority to, and the benefit of, U.S. provisional application entitled "INTRAOCULAR PRESSURE SENSING MATERIAL, DEVICES, AND USES THEREOF" having Ser. No. 62/687,614, filed Jun. 20, 2018, both of which are herein incorporated by reference in their entireties.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with Government support under HDTRA-1-15-1-0022 awarded by the Department of Defense/Defense Threat Reduction Agency. The Government has certain rights in this invention.

BACKGROUND

[0003] Measurement of intraocular pressure is important for glaucoma and many eye diseases. Currently, indirect methods are used for measuring intraocular pressure which involve external contact to the eye. However, the results are variable based upon the corneal thickness and other structural differences in the wall of the eye. As such, there exists a need for improved eye monitoring devices and techniques.

SUMMARY

[0004] In embodiments of the present disclosure, disclosed herein are intraocular implants. Intraocular implants as described herein can comprise a pressure-responsive material, the pressure-responsive material comprising chromogenic photonic crystals, wherein the chromogenic photonic crystals change confirmation resulting in a change of color of the pressure-responsive material in response to an amount of pressure exerted on the shape-memory chromogenic photonic crystals.

[0005] In embodiments according to the present disclosure, the pressure-responsive material can be a first color at a normal physiologic intraocular pressure of about 10 to about 20 mm Hg. The pressure-responsive material can be second color at an elevated intraocular pressure of greater than about 20 mm Hg. The pressure-responsive material can be a third color at a reduced intraocular pressure of less than about 10 mm Hg.

[0006] In embodiments according to the present disclosure, the implant can be an intraocular lens. In embodiments according to the present disclosure, the implant can be a glaucoma drainage device.

[0007] In embodiments according to the present disclosure, the pressure responsive material can be coated on a surface of a drainage tube of the glaucoma drainage device.

[0008] In embodiments according to the present disclosure, the surface can be an outer surface of the drainage tube. In embodiments according to the present disclosure, the surface can be an inner surface of the drainage tube.

[0009] In embodiments according to the present disclosure, the implant can comprise one or more layers of the pressure-responsive material coated on all or part of a surface of the implant or component thereof.

[0010] In embodiments according to the present disclosure, each of the one or more layers is about 0.5 mm to about 3 mm thick.

[0011] In embodiments according to the present disclosure, the pressure-responsive material can be integrated with a component of the implant.

[0012] In embodiments according to the present disclosure, the implant can comprise one or more layers of the pressure-responsive material embedded in all or part of a surface of the implant or component thereof. In other embodiments, the implant can include the pressure-responsive material in the body of the implant.

[0013] In embodiments according to the present disclosure, the pressure responsive material can comprise photonic crystals embedded in (e.g. encapsulated in) a hydrogel.

[0014] Also described herein are methods. In embodiments according to the present disclosure, methods as described herein comprise: implanting into the eye of a subject in need thereof an implant according to the present disclosure.

[0015] In embodiments according to the present disclosure, methods can further comprise detecting the color of the pressure-responsive material of the implant without contacting the eye.

[0016] In embodiments according to the present disclosure, methods can further comprise quantitatively measuring the color of the pressure-responsive material of the implant using a spectrometer.

[0017] In embodiments according to the present disclosure, a subject in need thereof can be a human or a canine. In embodiments according to the present disclosure, the subject in need thereof has or is at risk for ocular hypertension. In embodiments according to the present disclosure, the subject in need thereof has glaucoma.

[0018] In embodiments according to the present disclosure, a method of measuring intraocular pressure in a subject having an implant is described herein, the method comprising: detecting the color of the pressure-responsive material of the implant without contacting the eye. The subject can be a human or a canine. The subject can have ocular hypertension or can be at risk for ocular hypertension. The subject in need thereof can have glaucoma.

[0019] In embodiments according to the present disclosure, methods as described herein can comprise quantitatively measuring the color of the pressure-responsive material of the implant using a spectrometer or other spectral monitoring device, for example a smartphone with an application configured for spectrometry.

DETAILED DESCRIPTION

[0020] Before the present disclosure is described in greater detail, it is to be understood that this disclosure is not limited to particular embodiments described, and as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

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

[0023] All publications and patents cited in this specification are cited to disclose and describe the methods and/or materials in connection with which the publications are cited. All such publications and patents are herein incorporated by references as if each individual publication or patent were specifically and individually indicated to be incorporated by reference. Such incorporation by reference is expressly limited to the methods and/or materials described in the cited publications and patents and does not extend to any lexicographical definitions from the cited publications and patents. Any lexicographical definition in the publications and patents cited that is not also expressly repeated in the instant application should not be treated as such and should not be read as defining any terms appearing in the accompanying claims. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present disclosure is not entitled to antedate such publication by virtue of prior disclosure. Further, the dates of publication provided could be different from the actual publication dates that may need to be independently confirmed.

[0024] As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present disclosure. Any recited method can be carried out in the order of events recited or in any other order that is logically possible.

[0025] Embodiments of the present disclosure will employ, unless otherwise indicated, techniques of molecular biology, microbiology, organic chemistry, biochemistry, physiology, cell biology, cancer biology, and the like, which are within the skill of the art. Such techniques are explained fully in the literature.

Definitions

[0026] As used herein, "about," "approximately," and the like, when used in connection with a numerical variable, can generally refers to the value of the variable and to all values of the variable that are within the experimental error (e.g., within the 95% confidence interval for the mean) or within +/−10% of the indicated value, whichever is greater.

[0027] The term "biocompatible", as used herein, refers to a material that along with any metabolites or degradation products thereof that are generally non-toxic to the recipient and do not cause any significant adverse effects to the recipient. Generally speaking, biocompatible materials are materials that do not elicit a significant inflammatory or immune response when administered to a patient.

[0028] As used herein, "organism", "host", and "subject" refers to any living entity comprised of at least one cell. A living organism can be as simple as, for example, a single isolated eukaryotic cell or cultured cell or cell line, or as complex as a mammal, including a human being, and animals (e.g., vertebrates, amphibians, fish, mammals, e.g., cats, dogs, horses, pigs, cows, sheep, rodents, rabbits, squirrels, bears, primates (e.g., chimpanzees, gorillas, and humans).

[0029] As used herein, the terms "treating" and "treatment" can refer generally to obtaining a desired pharmacological and/or physiological effect. The effect can be, but does not necessarily have to be, prophylactic in terms of preventing or partially preventing a disease, symptom or condition thereof, such as abnormal eye pressure and/or diseases and conditions associated with abnormal eye pressure (including but not limited to glaucoma). The effect can be therapeutic in terms of a partial or complete cure of a disease, condition, symptom or adverse effect attributed to the disease, disorder, or condition. The term "treatment" as used herein covers any treatment of glaucoma, ocular hypertension (elevated intraocular eye pressure), or reduced intraocular eye pressure, in a subject, particularly a human or a canine, and can include any one or more of the following: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; and (c) relieving the disease, i.e., mitigating or ameliorating the disease and/or its symptoms or conditions. The term "treatment" as used herein can refer to both therapeutic treatment alone, prophylactic treatment alone, or both therapeutic and prophylactic treatment. Those in need of treatment (subjects in need thereof) can include those already with the disorder and/or those in which the disorder is to be prevented. As used herein, the term "treating", can include inhibiting the disease, disorder or condition, e.g., impeding its progress; and relieving the disease, disorder, or condition, e.g., causing regression of the disease, disorder and/or condition. Treating the disease, disorder, or condition can include ameliorating at least one symptom of the particular disease, disorder, or condition, even if the underlying pathophysiology is not affected, such as treating the pain of a subject by administration of an analgesic agent even though such agent does not treat the cause of the pain.

[0030] Discussion

[0031] Measurement of intraocular pressure is important for diagnosis and treatment of glaucoma and many other eye diseases. Currently, indirect methods are used for measuring intraocular eye pressure. These methods involve external eye contact to the eye. Thus, current methodologies produce results that are variable and based upon the corneal thickness and other structural differences in the wall in the eye that can change over time. As such, current methodologies can produce inaccurate results which can negatively impact eye health evaluations and disease monitoring and treatment.

[0032] With that said, described herein are materials, which can be biocompatible, that can be pressure-responsive and incorporated in intraocular lenses and/or other eye devices that can be capable of monitoring eye pressure. The materials can be capable of changing color in response to pressure exerted on the material. The color of the material

can be quantitatively measured and can provide a direct and non-contact method of measuring intraocular pressure. Other compositions, compounds, methods, features, and advantages of the present disclosure will be or become apparent to one having ordinary skill in the art upon examination of the following drawings, detailed description, and examples. It is intended that all such additional compositions, compounds, methods, features, and advantages be included within this description, and be within the scope of the present disclosure.

[0033] Described herein are devices that can be implanted into a subject, such as in the eye or eye region, that can include a pressure-responsive material. The pressure responsive material can be composed of chromogenic photonic crystals that can be based on smart shape memory polymers. The chromogenic photonic crystals can be as described in Leo, S. et al. 2018. Chromogenic Photonic Crystal Sensors Enabled by Multistimuli-Responsive Shape Memory Polymers" Small 14(12):1703515, which is incorporated by reference as if fully set forth herein. In embodiments according to the present disclosure, chromogenic photonic crystal sensors are based on smart shape memory polymers (SMPs) comprising polyester/polyether-based urethane acrylates blended with tripropylene glycol diacrylate, which exhibit nontraditional all-room-temperature shape memory (SM) effects.

[0034] The pressure-responsive material can change color when different pressures are exerted on it. Thus, when incorporated in a device that is implanted into an eye, the intraocular pressure can be exerted on the pressure-responsive material incorporated in the device. The pressure-responsive material can change confirmation depending on the amount of pressure exerted on it by the eye contents and thus be a particular color depending on that exerted pressure. The color can be qualitatively measured by shining a light into the eye and onto the pressure-responsive material implanted in the eye and observing the color of the pressure-responsive material. The color can be measured quantitatively using spectral analysis to determine the color of the pressure-responsive material. Any suitable device that can externally measure the color spectrally can be used. In some aspects, the device is a hand held spectrometer or smartphone with an imaging device. Such devices are generally known and available. For example, a color analysis app (e.g., Color Mate Version 1.2.2) installed on a smartphone can be used in analyzing the RGB values of the sensor in response to different intraocular pressures.

[0035] The color of the pressure-responsive material can be tuned by including silica particles with different diameters. Experiments have confirmed that the pressure-responsive materials of the present disclosure and devices including the pressure-responsive material can cover the whole visible spectrum range from 400 to 700 nm. For example, by including silica particles having an average diameter of about 500 to 500 nm, about 400 to 450 nm, and about 600 to 650 nm in the same pressure-responsive material, the material can appear green, blue, and red, respectively. The visible color can correlate to a pressure.

[0036] The color of the pressure-responsive material can be directly correlated to the intraocular pressure. In some aspects, at normal physiologic intraocular pressure (about 10 to about 20 mm Hg) the color of the pressure-responsive material can range from about 500 nm to 550 nm corresponding to a green color. The color of the pressure-responsive material can range be a first color. An intraocular pressure that is above normal (elevated intraocular eye pressure) can be anything over about 20 mm Hg. At elevated intraocular pressures ranging from about 20 mm Hg to about 30 mm Hg or more, the color of the pressure-responsive material can be a second color that is different from that at normal physiological pressure. The color of the pressure-responsive material can range from about 400 nm to 450 nm corresponding to a blue color. If a subject is not having symptoms of an eye disease such as glaucoma but has an elevated intraocular pressure, this can be referred to as ocular hypertension. These individuals are at risk for developing an eye disease, such as glaucoma, and can require more intensive monitoring.

[0037] Ocular hypertension is not the only pressure abnormality that can lead to eye problems. In some cases, such as after eye surgery (e.g. glaucoma surgery) or episodes of ocular ischemia, the intraocular pressure can become too low. A condition called hypotony can be diagnosed if the intraocular pressure decreases to about 6 mm Hg or less or in some cases about 10 mm Hg or less. When intraocular pressure is too low it can cause distortions of the retina, lens, and cornea that can degrade vision and lead to vision loss. At reduced intraocular pressures ranging from about 4 mm Hg to about 10 mm Hg, the color of the pressure-responsive material can be a third color that is different than the color at normal physiological pressure or elevated pressure. The color of the pressure-responsive material can range from about 600 nm to 650 nm corresponding to a red color.

[0038] As described above, the pressure-responsive material can be coated in one or more layers on or incorporated into at least a portion of an implantable intraocular device. The pressure-responsive material can be coated on or incorporated into at least a portion of an intraocular lens or other prosthetic devices. In some aspects, a layer of the pressure-responsive material can range from about 0.1 mm to 0.5 mm, 0.5 mm to about 3 mm, about 1 mm to about 2.5 mm, about 1.5 mm to about 2 mm thick. Suitable intraocular lenses and prosthetics are generally known and available.

[0039] The implantable device can include the pressure-responsive material in the body of the implant. In the case of an intra-ocular lens implant, for example, the pressure-responsive material could be placed in the outer part of the optic, thus leaving the central visual axis clear of any color change or potentially different refractive index material to prevent or minimize visual clarity issues while still undergoing pressure-responsive color change.

[0040] Glaucoma can be treated by implanting a device that helps keep the surgically-created drainage opening from healing and closing down. Many incorporate a tube through which the aqueous eye fluid passes. Others are solid and promote the flow of fluid along the surface of the implant. Newer implants commonly referred to as micro-invasive glaucoma surgery devices are tiny drainage implants (e.g. the Cypass Microstent from Alcon, AqueSys's XEN Gel Stent, MicroShunt Glaucoma Drainage System by InnFocus Inc., STARflo Glaucoma Implant and MlNlject from iSTar Madical SA, and the Hydrus Microstent form Ivantis) have also been developed and incorporate tiny drainage conduits (e.g. stents) that can create a permanent conduits for moving eye fluids and decreasing intraocular pressure. Other various implants for treatment of glaucoma are known. The pressure-responsive material can be coated on or incorporated in any of the components of an implant for treatment of

glaucoma. In some aspects the pressures-responsive material can be incorporated on or on the inside of the drainage stent or tube of the implant.

[0041] In use, the pressure-responsive material can be coated on an existing eye implant device described above. In other aspects, the pressure-responsive material can be coated on or otherwise incorporated in an eye implant device at the point of manufacture of the device or any of its components or material. The eye implant device can be inserted into an eye of a subject using any suitable surgical technique that is appropriate for that particular eye implant and subject. This can be determined by the medical practitioner. After implantation, the pressure of the subject's eye containing the eye implant device can be measured qualitatively by viewing the color of the pressure-responsive material using suitable eye examination devices and equipment (e.g. ophthalmoscope, ophthalmic lope, otoscopes, etc.) and/or qualitatively by using a suitable spectrophotometer device. These are discussed elsewhere herein. The method of pressure measurement when the pressure-responsive material and devices incorporating the pressure-responsive material is employed does not require contact with the eye or subject to changes in the structures of the eye. Further, this measurement method does not require any eye dilation or other uncomfortable procedures to allow measurement. Further, the devices herein allow for measurement of eye pressure at any time. This can be an advantage of current techniques as the pressure of the eye can change throughout the day. The devices and techniques described herein can thus allow for improved monitoring of the eye, particularly a diseased eye, and improve care of the subject.

[0042] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Publications cited herein and the materials for which they are cited are specifically incorporated by reference.

[0043] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

We claim:

1. An intraocular implant comprising:

a pressure-responsive material, the pressure-responsive material comprising chromogenic photonic crystals, wherein the chromogenic photonic crystals change conformation resulting in a change of color of the pressure-responsive material in response to an amount of pressure exerted on the shape-memory chromogenic photonic crystals and wherein the chromogenic photonic crystal comprise smart shape memory polymers (SMPs), wherein the implant is an intraocular lens.

2. The intraocular implant of claim **1**, wherein the pressure-responsive material is a first color at a normal physiologic intraocular pressure of about 10 to about 20 mm Hg, wherein the first color ranges from about 500 nm to 550 nm corresponding to a green color.

3. The intraocular implant of claim **2**, wherein the pressure-responsive material is a second color at an elevated intraocular pressure of greater than about 20 mm Hg, wherein the second color ranges from about 400 nm to 450 nm corresponding to a blue color.

4. The intraocular implant of claim **3**, wherein the pressure-responsive material is a third color at a reduced intraocular pressure of less than about 10 mm Hg, wherein the third color ranges from about 600 nm to 650 nm corresponding to a red color.

5. An intraocular implant comprising:

a pressure-responsive material, the pressure-responsive material comprising chromogenic photonic crystals, wherein the chromogenic photonic crystals change conformation resulting in a change of color of the pressure-responsive material in response to an amount of pressure exerted on the shape-memory chromogenic photonic crystals and wherein the chromogenic photonic crystal comprise smart shape memory polymers (SMPs), wherein the implant is a glaucoma drainage device.

6. The intraocular implant of claim **5**, wherein the pressure responsive material is coated on a surface of a drainage tube of the glaucoma drainage device.

7. The intraocular implant of claim **6**, wherein the surface is an outer surface of the drainage tube.

8. The intraocular implant of claim **6**, wherein the surface is an inner surface of the drainage tube.

9. An intraocular implant comprising:

a pressure-responsive material, the pressure-responsive material comprising chromogenic photonic crystals, wherein the chromogenic photonic crystals change conformation resulting in a change of color of the pressure-responsive material in response to an amount of pressure exerted on the shape-memory chromogenic photonic crystals and wherein the chromogenic photonic crystal comprise smart shape memory polymers (SMPs), wherein the implant comprises one or more layers of the pressure-responsive material embedded in all or part of a surface of the implant or component thereof.

10. An intraocular implant comprising:

a pressure-responsive material, the pressure-responsive material comprising chromogenic photonic crystals, wherein the chromogenic photonic crystals change conformation resulting in a change of color of the pressure-responsive material in response to an amount of pressure exerted on the shape-memory chromogenic photonic crystals and wherein the chromogenic photonic crystal comprise smart shape memory polymers (SMPs), wherein the implant comprises one or more layers of the pressure-responsive material coated on all or part of a surface of the implant or component thereof.

11. The intraocular implant of claim **10**, wherein each of the one or more layers is about 0.5 mm to about 3 mm thick.

12. An intraocular implant comprising:

a pressure-responsive material, the pressure-responsive material comprising chromogenic photonic crystals, wherein the chromogenic photonic crystals change conformation resulting in a change of color of the pressure-responsive material in response to an amount of pressure exerted on the shape-memory chromogenic photonic crystals and wherein the chromogenic photonic crystal comprise smart shape memory polymers (SMPs), wherein the pressure-responsive material is integrated with a component of the implant.

13. An intraocular implant comprising:

a pressure-responsive material, the pressure-responsive material comprising chromogenic photonic crystals, wherein the chromogenic photonic crystals change conformation resulting in a change of color of the pressure-responsive material in response to an amount of pressure exerted on the shape-memory chromogenic photonic crystals and wherein the chromogenic photonic crystal comprise smart shape memory polymers (SMPs), wherein the pressure-responsive material comprises a hydrogel.

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