human and porcine sclera *in vitro* (Wollensak, G. & Spoerl, E. Collagen crosslinking of human and porcine sclera. Journal Of Cataract And Refractive Surgery 30, 689-695 (2004)). Glutaraldehyde, glyceraldehyde, and riboflavin-UVA treatments increased Young's modulus by 122%, 34%, and 29% respectively compared to untreated controls. Since they are not light-activated, the authors report that it might be difficult to spatially control the cross linking effects of both glutaraldehyde and glyceraldehyde. Unwanted cross-linking of collagen in vascular and neural structures might have particularly untoward effects. Use of light activated riboflavin would seem preferable in this regard; however, UVA light is potentially cytotoxic and comparable exposures in the cornea to treat keratoconus require 30 minute irradiations (Wollensak G. Crosslinking treatment of progressive keratoconus: new hope. Curr Opin Ophthalmol. 2006;17(4):356-60). While cross-linking of scleral stromal components in the posterior pole would increase scleral modulus and potentially arrest myopic progression, there remains a need for a non-toxic cross-linking agent that could be activated using short exposure to a less toxic light source.

[0016] U.S. Published Application No. 20050271590, the contents of which are incorporated herein by reference, discloses methods of using crosslinking chemicals to covalently connect scleral collagen and/or other scleral proteins to increase scleral tensile strength or modulus. This approach utilizes chemical crosslinkers, some with undesirable toxicity profiles, by caging the chemicals in photo-labile structures which are disrupted to release the crosslinker chemicals in a controlled manner, thereby limiting the area of exposure and in some instances toxicity effects.

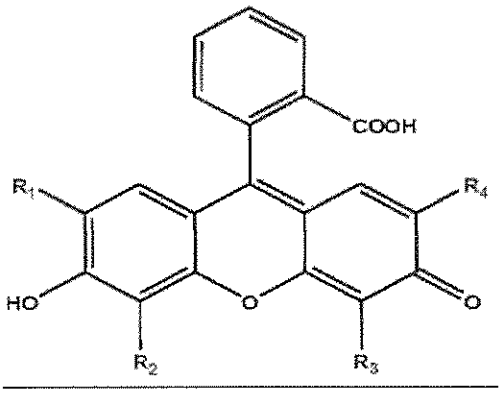
[0017] Given the limitations of current therapies for treating keratoconus and myopia, new therapies without such limitations are needed. The present invention fulfills this need.

Summary ~~of the Invention~~

[0018] The present disclosure~~invention~~ concerns a therapy for affecting one or more mechanical and/or chemical properties of a body tissue in an individual. In specific embodiments, the present disclosure~~invention~~ concerns one or more photochemical therapies for affecting one or more mechanical and/or chemical properties of a body tissue in an individual. The

therapy may be for any tissue in the body, including at least an ocular tissue, a blood vessel wall, aveolar structures (e.g. in COPD patients), and damaged heart tissue, e.g., for the mitigation of

dilated cardiomyopathies. In particular embodiments, the therapy is used for an ocular tissue. Exemplary ocular tissues include at least the cornea, sclera, optic nerve, trabecular meshwork, conjunctiva, choroid, and subretinal space. In an aspect, there is provided the use of a composition comprising a photoinitiator compound in the manufacture of a medicament for directly altering a mechanical and/or chemical property of an ocular tissue in a subject, wherein the photoinitiator compound comprises a photoinitiator, a PEG-photoinitiator, or a combination thereof, wherein the photoinitiator is selected from 2-hydroxy-1-[4-(2-hydroxyethoxy)phenyl]-2-methyl-1-propanone and a compound having the structure of Formula I:



wherein R_1, R_2, R_3, and R_4 are each Br or pharmaceutical salts thereof,

wherein the composition does not include a photopolymerizable compound, and

wherein the photoinitiator compound is activated by a visible light irradiation of the ocular tissue to directly alter a mechanical and/or chemical property of the ocular tissue, and the subject has or is at risk of developing an ocular deformation condition comprising one or more of keratoconus, post-laser-assisted in situ keratomileusis (LASIK) ectasia, post-photorefractive keratectomy (PRK) ectasia, post-infection ectasia, peripheral ectasia, rheumatoid condition of the cornea, degenerative myopia, regular myopia, scleral staphyloma, ocular hypertension glaucoma, or low tension glaucoma.

[0019] In specific embodiments, the present disclosure~~invention~~ employs a therapy that is an improvement upon particular therapies for certain ocular applications. In further specific embodiments, the present disclosure~~invention~~ improves upon *uv*-irradiation treatments for crosslinking of tissues, such as the cornea or sclera, for example. Such a treatment would have one or more of the following exemplary specifications: 1) a photoinitiator compound that can be activated with visible light to affect the mechanical and/or chemical properties of a tissue, such as improve the mechanical properties of the cornea to resist progressive ectasia, for example; 2) the photoinitiator compound may be introduced with minimal pain and/or minimal risk; 3) the photoinitiator compound is non-toxic to ocular structures; 4) photoinitiator compound

activation occurs with safe levels of irradiation; 5) photoinitiator compound activation occurs with less than or equal to 30 minutes irradiation, for example.

[0020] In particular embodiments of the disclosure~~invention~~, the present disclosure~~invention~~ provides one or more of the following needs: 1) an effective photoinitiator compound for strengthening a tissue (such as the cornea or sclera, for example) is demonstrated that has low toxicity and is activated by visible light; 2) improved photoinitiator compounds or derivatives thereof that are capable of administration routes that obviate the need to remove epithelium (such as for keratoconus treatment of a cornea) are described, including, for example, (a) topical application of drug that itself, or after modification, can cross the corneal epithelium in sufficient concentration to reach the corneal stroma in a therapeutically effective amount; and/or (b) injection of drug into the stroma using a fine-gauge needle; and/or 3) reduced irradiation duration using light applied for about 30 minutes or less is demonstrated to affect the tissue, such as to stabilize the shape of the cornea, for example.

[0021] Exemplary applications of the present disclosure~~invention~~ for ocular needs are provided. In particular embodiments, the present disclosure~~invention~~ is employed for the cornea, including the following: preventing the need for cornea transplant (keratoplasty) by halting progression of keratoconus and other corneal ectasias such as post-LASIK ectasia, pellucid marginal degeneration; enabling patients with keratoconus or other corneal degenerations to safely undergo refractive surgery; and/or stabilizing corneal shape after refractive surgery, particularly

if keratoconus becomes manifested afterward. The present disclosure~~invention~~ also provides means for stabilization of tissue anywhere in the eye, including for example the sclera, using light-activated crosslinking with visible light.

[0022] Although in particular embodiments the disclosure~~invention~~ employs visible light, in alternative embodiments, the present disclosure~~invention~~ utilize ultraviolet or infrared light. In further specific embodiments, the present disclosure~~invention~~ also applies to photoinitiator activation using two-photon or multi-photon activation.

[0023] In certain embodiment~~aspects~~ of the present disclosure~~invention~~, the photoinitiator compound is employed to affect crosslinking among the constituent molecules in an endogenous tissue in a subject.

[0024] Some embodiments herein are a method of altering a mechanical and/or chemical property of a tissue in a subject comprising the steps of:

a) providing a photoinitiator compound to a tissue of the subject, and

b) activating the photoinitiator compound by a visible light irradiation of the tissue,

whereby the photoinitiator compound directly alters a mechanical and/or chemical property of the tissue.

[0025] Some embodiments herein are the method of paragraph [0024] wherein the method is further defined as strengthening the tissue, stabilizing the tissue shape, changing the shape of the tissue, or a combination thereof.

[0026] Some embodiments herein are the method of paragraph [0024] or [0025] wherein the tissue is an ocular tissue.

[0027] Some embodiments herein are the method of paragraphs [0024] to [0026] wherein the ocular tissue includes at least a portion of a cornea and/or a sclera.

[0028] Some embodiments herein are the method of paragraphs [0024] to [0027] wherein the ocular tissue includes at least a portion of a lamina cribrosa.

[0029] Some embodiments herein are the method of paragraphs [0024] to [0028] wherein the tissue includes at least a portion of the cornea, the method is performed substantially

[0045] Some embodiments herein are the method of paragraphs [0038] to [0044] wherein the photoinitiator compound comprises a polyethylene glycol derivative of a compound represented by Formula I.

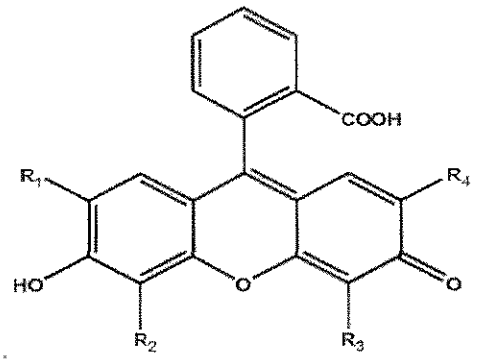
[0046] Some embodiments herein are the method of paragraphs [0038] to [0045] wherein the photoinitiator compound is capable of directly treating the ocular deformation condition upon illumination of the photoinitiator compound for 30 minutes or less using light comprising a wavelength of 500±50 nm at an illumination intensity of from 1-100 mW/cm^2.

[0047] Some embodiments herein are the method of paragraphs [0038] to [0046] wherein the photoiniator is provided by topical administration.

[0048] Some embodiments herein are the method of paragraphs [0038] to [0047]wherein the photoiniator is provided by injection.

[0049] Some embodiments herein are the method of paragraphs [0038] to [0048] wherein the ocular tissue includes at least a portion of the cornea, the method is performed substantially concurrently with a corneal operation and the photoinitiator is provided in a therapeutically effective amount which directly reduces the risk of a post operative corneal *deformation condition.*

[0049a] In another aspect, there is provided the use of a composition comprising a photoinitiator compound in a therapeutically effective amount in the manufacture of a medicament for treating or reducing the risk of an ocular deformation condition in a subject, wherein the composition does not include a photopolymerizable compound, wherein the medicament directly treats, or directly reduces the risk of an ocular deformation condition in an ocular tissue of the subject; and wherein the photoinitiator compound comprises a photoinitiator, a PEG-photoinitiator, or a combination thereof, wherein the photoinitiator is selected from 2-hydroxy-1-[4-(2-hydroxyethoxy)phenyl]-2-methyl-1-propanone and a compound having the structure of Formula I:



wherein R_1, R_2, R_3, and R_4 are each Br or pharmaceutical salts thereof, and wherein the photoinitiator compound is activated by a light irradiation of the ocular tissue to directly treat or directly reduce the risk of the ocular deformation condition.

[0050] Some embodiments herein are a use of a photoinitiator compound for manufacturing a medicament for a direct treatment or prevention of an ocular deformation condition by the photoinitiator compound.

[0051] Some embodiments herein are a photoinitiator compound for use as a medicament for directly treating or reducing the risk of an ocular deformation condition.

[0052] Some embodiments herein are the use according to any of the preceding paragraphs [0050] to [0051] wherein the direct treatment, prevention or reduction of the risk of the ocular deformation condition comprises an increased modulus of an ocular tissue.

[0053] Some embodiments herein are the use according to paragraph [0052] wherein the ocular tissue includes at least a portion of the sclera and/or the cornea and optionally includes the entirety of the sclera and/or the cornea.