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(54) **Title:** LASER INDUCED REFRACTIVE INDEX CHANGE METHOD AND OPHTALMIC PRODUCT TREATED BY SAID METHOD

(57) **Abstract:** A method of forming a silk fibroin containing optical device with a modified refractive index pattern provided therein includes: providing an optical device comprising an ophthalmic material made primarily of silk fibroin; and forming at least one laser-modified pattern within the optical device by exposing regions of the ophthalmic material to light pulses from a laser to cause changes in the ophthalmic material in the exposed regions sufficient to cause a change in refractive index of the exposed regions relative to the refractive index of the ophthalmic material in non-exposed regions. The laser exposure may be performed by scanning focused pulses from the laser along regions of the ophthalmic material. The ophthalmic material may comprise a silk fibroin hydrogel material. The silk fibroin hydrogel material may be obtainable by polymerizing one or more hydrophilic monomers and silk fibroin in the presence of a copolymerization initiator.

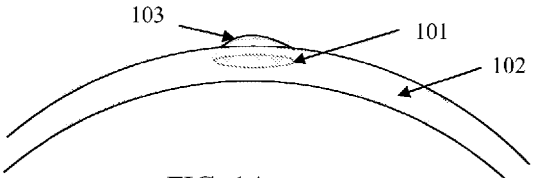


FIG. 1A

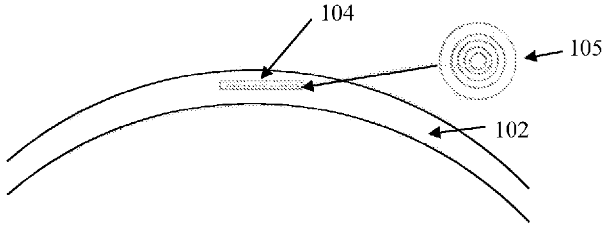


FIG. 1B

LASER INDUCED REFRACTIVE INDEX CHANGE METHOD AND OPHTALMIC PRODUCT TREATED BY SAID METHOD

RELATED FIELDS

[0001] Femtosecond micromachining for inducing refractive index (RI) or phase change in ophthalmic materials.

BACKGROUND

[0002] Femtosecond micromachining is a process that uses femtosecond lasers to deliver a large amount of energy to a small area, creating localized changes in a material's properties. By scanning a tightly focused pulse in the material, a wide range of nano- and microstructures can be inscribed in metals, plastics, ceramics, and biological tissues. This technique is often used in the production of microfluidic devices, and other microscale components for various purposes, including data storage, drug delivery, and environmental monitoring. Furthermore, when the pulse energy is below the ablation threshold, femtosecond lasers can be used to create localized refractive index changes in transparent materials without the damage or removal of the material.

[0003] This technique has more recently been applied to alter the optical properties of ophthalmic materials, such as hydrogel-based contact lenses, intra-ocular lenses (IOL), and cornea tissues, by creating different refractive index shaping structures for vision correction applications. LIRIC (Laser Induced Refractive Index Change) writing is a process that uses femtosecond laser pulses, at energies below the damage threshold, to locally modify the refractive index of ophthalmic materials via multiphoton absorption. Gandara-Montano *et al.* ("Femtosecond laser writing of freeform gradient index micro-lenses in hydrogel-based contact lenses," Optical Materials Express 5(10), 2257–2271 (2015)), e.g., successfully wrote arbitrary Zernike polynomials in hydrogel-based contact lenses. A phase-wrapped lens was written directly inside an IOL to alter the hydrophilicity of targeted areas, and also high-quality gradient-index (GRIN) Fresnel lenses with wide power range from -3.0 to +1.5 diopters were written in plano contact lens materials. NIR/Blue femtosecond lasers have further been used for noninvasive Intra-Tissue Refractive Index Shaping (IRIS) inside corneal tissue.

[0004] U.S. Publication No. 2008/0001320, the disclosure of which is incorporated herein by reference in its entirety, more particularly describes methods for modifying the refractive index of optical polymeric materials, such as intraocular lenses, corneal inlays, or contact lenses, using very short pulses from a visible or near-IR laser having a pulse energy from, e.g., 0.5 nJ to 1000 nJ, where the intensity of light is sufficient to change the refractive index of the material within the focal volume, whereas portions just outside the focal volume are minimally affected by the laser light. Irradiation within the focal volume results in refractive optical structures characterized by a change in refractive index of 0.005 or more relative to the index of refraction of the bulk (non-irradiated) polymeric material. Under certain irradiation conditions and in certain optical materials, a change in refractive index of 0.06 was measured. The change in refractive index can be used to form patterned desired refractive structures in the optical polymeric material.

[0005] U.S. Publication No. 2012/0310340, the disclosure of which is incorporated herein by reference in its entirety, further describes a method for providing changes in refractive power of an optical device made of an optical, polymeric material by forming at least one laser-modified, gradient index (GRIN) layer disposed between an anterior surface and a posterior surface of the device by scanning with light pulses from a visible or near-IR laser along regions of the optical, polymeric material. The at least one laser-modified GRIN layer comprises a plurality of adjacent refractive segments, and is further characterized by a variation in index of refraction of at least one of: (i) a portion of the adjacent refractive segments transverse to the direction scanned; and (ii) a portion of refractive segments along the direction scanned.

[0006] Huang and Knox ("Femtosecond micro-machining of hydrogels: parametric study and photochemical model including material saturation," Optical Materials Express, Vol. 9, No. 9/1, 3818–3834 (2019)), further studied the optimization of laser writing system parameters in the LIRIC writing technique. They examined the effects of various laser system parameters, including the laser repetition rate, wavelength, pulse duration and shape, scan speed, numerical aperture, and average power, on the induced refractive index change in ophthalmic hydrogels. They developed a photochemical model given in equation (2) relating the phase change induced $\Delta\Phi$, a quantity related to refractive index change by equation (1), to various writing and material parameters.

[0007] $$\Delta\Phi = \frac{\Delta n \cdot L}{\lambda}, \qquad (1)$$

Where Δn is the refractive index change, L is the axial depth of the refractive index change region and λ is the wavelength of the He-Ne laser used in the interferometer to image the phase change.

[0008] $$\Delta\Phi = \gamma_m \frac{\beta_m \cdot P_{avg}^{m} \cdot NA^{2(m-2)} \cdot m^{m-2}}{\nu^{m-1} \cdot \tau^{m-1} \cdot \lambda^{2(m-1)} \cdot S \cdot t}, \qquad (2)$$

Where $\Delta\Phi$ is the induced phase change measured in waves at the measurement wavelength, NA is the numerical aperture, P_{avg} is average power, m is nonlinear absorption factor,β is the nonlinear absorption coefficient, v is repetition rate of the laser,τ is pulse width, λ is the laser wavelength, S is scan speed, t is linespacing and γ is material constant.

[0009] With the developed photochemical model, it is possible to carefully chose laser writing system parameters to induce desired refractive corrections to produce customized contact lenses.

[0010] While LIRIC procedures have been disclosed for writing vision correcting patterns in various known ophthalmic devices, for devices which are designed to be implanted or otherwise to come in direct contact with the eye, it is important that such devices are biocompatible and have long term stability while in contact with the eye. It would be desirable to be able to write corrective patterns by LIRIC in a new class of ophthalmic devices which may provide desirable biocompatibility and stability.

SUMMARY

[0011] In one embodiment of the disclosure, a method of forming a silk fibroin containing optical device with a modified refractive index pattern provided therein is described, where the method comprises: providing an optical device comprising an ophthalmic material made primarily of silk fibroin; and forming at least one laser-modified pattern within the optical device by exposing regions of the ophthalmic material to light pulses from a laser to cause changes in the ophthalmic material in the exposed regions sufficient to cause a change in refractive index of the exposed regions relative to the refractive index of the ophthalmic material in non-exposed regions.

[0012] In various further specific embodiments of the disclosure, the laser exposure may be performed by scanning focused pulses from the laser along regions of the ophthalmic material; the ophthalmic material may comprise a silk fibroin hydrogel material; the silk fibroin hydrogel material may be obtainable by polymerizing one or more hydrophilic monomers and silk fibroin in the presence of a copolymerization initiator; and/or the silk fibroin hydrogel material may be more particularly obtainable by polymerizing hydroxy ethyl methacrylate (HEMA), ethylene glycol dimethacrylate (EGDMA), and silk fibroin in the presence of a copolymerization initiator.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] Fig. 1A is an illustration of a corneal inlay inserted into a cornea to produce a “bump” in the cornea surface to add power.

[0014] Fig. 1B is an illustration of a nominally flat corneal inlay with add power written in the inlay by LIRIC inserted into a cornea to add power without producing a “bump” in the cornea surface.

[0015] Figs. 2A-2C illustrate placement of a silk material on exposed cornea stroma bed without performing LASIK ablation, and subsequent LIRIC laser writing of a correction pattern in the silk layer.

[0016] Figs. 3A-3C illustrate placement of a silk material on exposed cornea stroma bed after performing LASIK ablation, and subsequent LIRIC laser writing of a correction pattern in the silk layer.

[0017] Fig. 4 is a schematic illustrating a laser writing system employed in one embodiment of the disclosure.

[0018] Figs. 5A and 5B illustrate an interference pattern and corresponding retrieved phase shift obtained for a phase bar written in a silk-hydrogel composite material in one embodiment of the disclosure.

[0019] Fig. 6 is a bright field image of phase bars written in a silk-hydrogel material at varying scan speeds in an embodiment of the disclosure.

[0020] Fig. 7 is a schematic illustrating a second laser writing system employed in an embodiment of the disclosure.

[0021] Figs. 8A and 8B illustrate differential interference contrast in transmision mode (TDIC) and bright field microscopy in transmision mode (TBF) images for phase bars written in wet silk fibroin material material at varying average power in an embodiment of the disclosure.

[0022] Fig. 9A is a plot of the magnitude of phase shift induced versus the average writing power obtained in an embodiment of the disclosure.

[0023] Fig. 9B is a differential interference contrast in reflection mode (RDIC) image for phase bars written in a silk-hydrogel composite material at varying average power in an embodiment of the disclosure.

[0024] Figs. 10A and 10B illustrate bright field microscopy in reflection mode (TBF) and differential interference contrast in reflection mode (RDIC) and images for phase bars written in wet silk fibroin material material at varying scan speeds in an embodiment of the disclosure.

[0025] Figs. 10C and 10D illustrate an interference pattern and corresponding retrieved phase shift obtained for a phase bar written in hydrated silk material autoclaved in saline solution in one embodiment of the disclosure.

DETAILED DESCRIPTION

[0026] The following description is not to be taken in a limiting sense but is given solely for the purpose of describing the broad principles of the disclosure. Specific embodiments may be described by way of example.

[0027] The present disclosure is directed towards forming at least one laser-modified refractive index pattern within an optical device comprising an ophthalmic material made primarily of silk fibroin. Silk fibroin, a protein produced by the silkworm, is a natural compound and has been found to enhance the properties of synthetic polymers for eye implantation. It is transparent, biocompatible, and affordable. Silk fibroin is an FDA-approved biomaterial. By being made primarily of silk fibroin, it is meant that the ophthalmic material comprises at least 50 wt% silk fibroin. While laser-induced refractive index change patterns had not previously been written in materials comprising primarily silk fibroin, unique aspects of the present disclosure include demonstration that refractive index change patterns may be written in such materials, thus enabling optical devices including such refractive index change patterns which provide enhanced biocompatibility when implanted or otherwise in contact with the eye while in use. In particular embodiments, the present disclosure more specifically may be directed towards writing of laser-modified refractive index patterns in implantable optical devices comprising an ophthalmic material made primarily of silk fibroin, and in even more particular embodiments in such implantable optical devices which are designed for correcting presbyopia.

[0028] In the field of human vision correction, presbyopia affects everyone over the age of 50, reducing the eye’s ability to accommodate to near objects. Many potential solutions to the problem have been developed such as multifocal contact and intra-ocular lenses, artificial iris implants, progressive eyeglasses, adjustable glasses, presbyopic LASIK surgery, corneal inlays that increase curvature in the corneal center, or accommodating IOLs. We disclose a new kind of optical corrector for presbyopia made of highly manufacturable ophthalmic materials made of primarily silk fibroin which are biocompatible for human eye wear or implantation. The elements incorporate a vision corrector written with laser-induced refractive index change (LIRIC).

[0029] As people age, their ability to accommodate reduces predictably and steadily, due to the gradual stiffening of the human crystalline lens, as well as the gradual weakening of the ciliary muscles that normally act on the lens to change its shape in order to effect accommodation, or change in focal length in response to a defocusing stimulus.

[0030] Many kinds of approaches have been developed to alleviate the problem. These typically fall in the categories of alternating vision, such as those produced by glasses that change their refractive power over the visual field, known popularly as “progressive” glasses, multifocal or extended depth-of-focus (EDOF) optics, monovision (one eye corrected for far and another for near) and attempts at dynamic correction including spectacles with variable power or accommodating IOLs. Among the available corrections, multifocal optics, aiming at delivering two or more distances in focus, or extended-depth of focus have become the most popular, with numerous designs in the markets. Multifocal corrections can come in the form of a contact lens, where the refractive power of a contact lens can be varied over the diameter of the lens by controlling the shape of the surface. This results in an increased range of well-focused vision.

[0031] Perhaps the largest expansion of multifocal designs have been developed in the form of intraocular lenses. These can be implanted when a patient is having their crystalline lenses removed due to the formation of cataracts that are degrading their quality of vision. More recently, refractive lens exchange procedures may be performed even in presbyopic patients with clear crystalline lenses, where the lens is being replaced by an artificial implant that provides distance correction as well as visual functionality at near focus, generally using multifocal or extended-depth-of-focus IOL designs.

[0032] Recently, surgical treatments for presbyopia that preserve the transparent crystalline lens (along with some potential -albeit diminished- accommodation functionality) have been preferred in relatively young presbyopes. The treatments include Presbyopic LASIK where the cornea is sculpted to produce an increased power (near add) in the central cornea.

[0033] On the other hand, non-tissue subtraction refractive procedures are gaining traction. Unlike LASIK or Small Incision Lenticular Extraction (SMILE) procedures that eliminate corneal tissue, those would aim at inserting additional material to the cornea, or anterior segment in general (additive procedures). Procedures such as those aiming at changing the refractive properties of the tissue (such as LIRIC) will also fall into the category of non-tissue subtraction refractive procedures.

[0034] A further alternative to induce multifocality or EDOF without removing ocular tissue are corneal inlays. Those are lenticules with a prolate-shape inserted into a corneal incision to produce a “bump” in the cornea surface which can produce enhanced “add” power in the center of the cornea, such as the device called RAINDROP$^{\text{TM}}$. The use of a mechanical deformation to cause the add power in the central zone of the cornea involves some complex biomechanical issues, however, that may make the reproducibility and stability of the correction difficult.

[0035] Another alternative of “tissue adding” procedure without removing the crystalline lens is phakic IOLs. Those are implanted generally between the iris and the crystalline lens. They have been typically used to correct myopia in young high myopes, where a LASIK procedure would require large reductions in corneal thickness. Since the phakic IOL is implanted without removing the natural crystalline lens the accommodation functioning is intact. Recently phakic IOLs have been expanded to include EDOF designs catering the relatively young presbyopes. It is recognized that biocompatibility of these lenses poses more challenges, given the higher proximity to ocular structures. To address this challenge, a copolymer of collagen and Hema has been proposed. For instance, the market standard for phakic lens (ICLs, by Staar Surgical Optics) are made of collamer material, with 60% of polyhydroxy ethyl methacrylate (pHEMA), water (36%), benzophenone (3.8%), and 0.2% porcine collagen. The presence of collagen is claimed to have a positive effect in the hydrophilicity and exchange of gas and nutrients in the anterior chamber.

[0036] The present disclosure addresses the combined problems of complex biomechanical issues and biocompatibility by use of ophthalmic material comprising primarily silk fibroin and use of LIRIC femtosecond processing. In particular embodiments, such solution may more particularly be used to advantageously addresses existing problems in presbyopia correcting procedures.

[0037] As indicated above, the disclosure relates to writing of refractive index change patterns in an ophthalmic material comprising primarily silk fibroin. Silk fibroin is typically obtained from silk-cocoon in a known fashion, and may be solution cast to form a membrane. In a particularly preferred embodiment, the ophthalmic material comprising primarily silk fibroin may comprise a silk fibroin hydrogel material, and may be obtainable by polymerizing one or more hydrophilic monomers and silk fibroin in the presence of a copolymerization initiator. In various embodiments, the resulting silk hydrogel materials can be machined, molded or machined into, e.g., a contact lens, a corneal inlay, a phakic or a non-phakic IOL.

[0038] An ophthalmic material as described herein is understood as material that is suitable for ophthalmic applications, such as a hydrogel. An ophthalmic material as described herein may initially be substantially free of water upon formation, e.g., has less than 0.5 wt.% of water. In some embodiments, the ophthalmic material, e.g., when comprising hydrophilic monomers, may be hydrated upon addition of water to form a hydrated hydrogel. Accordingly, in various states the ophthalmic material may also be referred herein as to a dry ophthalmic material or dry hydrogel, and the hydrated hydrogel obtained may also be referred to as the hydrated ophthalmic material.

[0039] In specific embodiments, the ophthalmic material comprising primarily silk fibroin may be obtainable by polymerizing a first monomer and a second monomer in the presence of silk fibroin, as described in EP Appl. No. 23383047.0, filed October 11, 2023, wherein such materials are demonstrated to be bio-compatible and stable, well suited for ophthalmic applications such as ophthalmic lenses and/or implants and in particular for corneal inlay application. The first and second monomers are monomers suitable for polymerization and may be selected from monomers typically used in ophthalmic applications. More particularly, in such embodiments the first monomer and the second monomer are different from each other. As a mode of example, the first and second monomer may be independently selected from a methacrylate, an acrylate, an acrylamide, a siloxane, a carbamate, a glycol, a dialdehyde, a vinyl and an allyl.

[0040] In several embodiments the methacrylate may be selected from hydroxy ethyl methacrylate (HEMA), ethylene glycol dimethacrylate (EGDMA), methacrylic acid (MAA), methyl methacrylate (MMA), oligo (ethylene glycol) methyl ether methacrylate (OEGMA), glycerol methacrylate (GMA), isobutyl methacrylate (IBMA), allyl methacrylate (AMA), 3-[tris(trimethylsiloxy)silyl] propyl methacrylate (TRIS), polypropylene glycol dimethylacrylate (PPGDMA) and methacryloyl oxyethyl phosphorylcholine (MPC); more preferably may be selected from HEMA and EGDMA; and yet more preferably the first monomer may be HEMA and/or the second monomer may be EGDMA.

[0041] As a mode of example an acrylate may be ethylene glycol phenyl ether acrylate (EGPEA); an acrylamide may be selected from N,N-dimethylacrylamide (DMA), diacetone acrylamide (DAA) and methylene-bis-acrylamide (MBA); a siloxane may be dimethylsiloxane (DMS), a carbamate may be tris(trimethylsioxy)silyl) propyl vinyl carbamate (TPVC), a glycol may be selected from diethylene glycol (DEG) and polyethylene glycol dialdehyde (PEG-DA), a vinyl may be N-vinyl pyrrolidone (N-VP) and an allyl may be diallyl maleate (DA).

[0042] The first monomer may be preferably selected from a methacrylate such as HEMA, EGDMA, MAA, MMA, OEGMA, GMA, IBMA, AMA, TRIS; an acrylate such EGPEA; a methacrylamide DMA and DAA; a siloxane such as DMS; a carbamate such as TPVC; and a glycol such as DEG. Preferably the first monomer may be HEMA.

[0043] The second monomer may be preferably selected from a methacrylate such as EGDMA and PPGDMA; an acrylamide such as MBA; a glycol such as PEG-DA; a vinyl such as N-VP; and an allyl such as DA. Preferably the second monomer may be EGDMA.

[0044] In several particular embodiments the first and second monomer may be selected from hydrophilic monomers, in particular they may be selected from HEMA, EGDMA, EGPEA, DEG, and MPC, and more in particular from HEMA and EGDMA. In a preferred embodiment the first monomer is HEMA and/or the second monomer is EGDMA. In yet a preferred embodiment the first monomer is HEMA and the second monomer is EGDMA. The use of such monomers may advantageously provide an ophthalmic material suitable for forming a hydrogel.

[0045] An ophthalmic material comprising primarily silk fibroin as described herein may typically have a weight proportion of the combination of the first and second monomers of 10-40 wt.% and more in particular, 20-25 wt.%, and silk fibroin weight proportion of 60-90 wt.% and more particularly 75-80 wt.%, based on the total weight of first monomer, second monomer and SILK FIBROIN. Thus, such materials continue to comprise primarily silk fibroin.

[0046] An ophthalmic material as described for use herein obtainable from such reaction mixtures may typically have a weight ratio of the first monomer to the second monomer of greater than 1:1, e.g., from 2:1 to 40:1, in particular from 3:1 to 35:1, more in particular from 5:1 to 30:1, yet more in particular from 7:1 to 25:1.

[0047] Useful polymerization initiators may be selected, e.g., from azobisisobutyronitrile (AIBN), ammonium persulfate (APS), tetramethyl ethylenediamine (TEMED), and benzoyl peroxide (BP), and more preferably the polymerization initiator is AIBN. Such initiators are known in the art and may initiate the polymerization reaction by, e.g., application of heat.

[0048] As indicated above, in several embodiments, e.g., when the first and second monomers of the ophthalmic material, are selected from hydrophilic monomers, upon addition of water the ophthalmic material may form a hydrogel. In such embodiments, the hydrogel in hydrated form may comprise, e.g., 10 to 40 wt.% of water, in particular from 12 to 30 wt.% of water, based on the total weight of the hydrogel.

[0049] In various embodiments, the silk hydrogel materials can be machined, molded or machined into, e.g., a contact lens, a corneal inlay, a phakic or a non-phakic IOL. As indicated above and as described in more detail below, the ophthalmic material comprising primarily silk fibroin is well suited for ophthalmic lenses and/or implants. The ophthalmic material as such may be used in dry forms for the formation of said ophthalmic lenses and/or implants, or may be hydrated to form a hydrated hydrogel to form said ophthalmic lenses and/or implants.

[0050] In particular embodiments, desired refractive index change patterns may be formed in an ophthalmic material comprising primarily silk fibroin as described herein by irradiating the ophthalmic material with very short laser pulses of light as described in U.S. Publication Nos. 2008/0001320, 2009/0287306, 2012/0310340 and 2012/0310223. The femtosecond laser pulse sequence pertaining to an illustrative embodiment, e.g., operates at a high repetition-rate, e.g., 80 MHz, and consequently the thermal diffusion time (>0.1μs) is much longer than the time interval between adjacent laser pulses (~11 ns). Under such conditions, absorbed laser energy can accumulate within the focal volume and increase the local temperature.

[0051] Femtosecond laser pulse writing methods may be more advantageously carried out if the ophthalmic material further includes a photosensitizer, as more particularly taught in U.S. Publication Nos. 2009/0287306 and 2012/0310340. The presence of the photosensitizer permits one to set a scan rate to a value that is at least fifty times greater, or at least 100 times greater, than a scan rate without a photosensitizer present in the material, and yet provide similar amount of non-linear absorption in the focal volume. Alternatively, the use of a photosensitizer may permit one to set an average laser power to a value that is at least two times less, more particularly up to four times less, than an average laser power without a photosensitizer in the material, yet provide similar results. A photosensitizer having a chromophore with a relatively large multi-photon absorption cross section is believed to capture the light radiation (photons) with greater efficiency and then transfer that energy to the material within the focal volume. The photosensitizer may include, e.g., a chromophore having a two-photon, absorption cross-section of at least 10 GM between a laser wavelength range of 750 nm to 1100 nm. In the case of a non-polymerizable photosensitizer, solutions containing a photosensitizer may be prepared and the ophthalmic materials may be allowed to come in contact with such solutions to allow up-take of the photosensitizer into the matrix of the material. In the case of a polymerizable photosensitizer, monomers containing a chromophore, e.g., a fluorescein-based monomer, may be used in a monomer mixture used to form the ophthalmic material such that the chromophore becomes part of the resulting polymeric matrix. Further, one could use a solution containing a non-polymerizable photosensitizer to dope a material that had been prepared with a polymerizable photosensitizer. Also, it is to be understood that the chromophoric entities could be the same or different in each respective photosensitizer.

[0052] The concentration of a polymerizable, monomeric photosensitizer having a two-photon, chromophore in an ophthalmic material can be as low as 0.05 wt.% and as high as 10 wt.%. Exemplary concentration ranges of polymerizable monomer having a two-photon, chromophore in a hydrogel material is from 0.1 wt.% to 6 wt.%, 0.1 wt.% to 4 wt.%, and 0.2 wt.% to 3 wt.%. In various aspects, the concentration range of polymerizable monomer photosensitizer having a two-photon, chromophore in a hydrogel material is from 0.4 wt.% to 2.5 wt.%.

[0053] Due to the repetition rate pulse sequence used in the irradiation process, the accumulated focal temperature increase can be much larger than the temperature increase induced by a single laser pulse. The accumulated temperature increases until the absorbed power and the dissipated power are in dynamic balance. For hydrogel polymers, thermal-induced depolymerization can produce a change in the refractive index as the local temperature exceeds a transition temperature. If the temperature increase exceeds a second threshold, a somewhat higher temperature than the transition temperature, the polymer is pyrolytically degraded and carbonized residue and water bubbles are observed. In other words, the material exhibits visible optical damage (scorching). Each of the following experimental parameters such as laser repetition rate, laser wavelength and pulse energy, TPA coefficient, and water concentration of the materials should be considered so that a desired change can be induced in the hydrogel polymers without optical damage.

[0054] The pulse energy and the average power of the laser, and the rate at which the irradiated regions are scanned, will in-part depend on the specific composition of the material that is being irradiated, how much energy absorption is required to create a desired refractive index change in the material. The selected pulse energy will also depend upon the scan rate and the average power of the laser at which the refractive index change features are written into the material.

Typically, greater pulse energies will be needed for greater scan rates and lower laser power. For example, some materials will call for a pulse energy from 0.05 nJ to 100 nJ or from 0.2 nJ to 10 nJ.

[0055] In particular embodiments, a Fresnel-type phase wrapped refractive index profile may be written into the silk-optical material, in any of the above-mentioned platforms.

[0056] For contact lenses, an advantage of the use of ophthalmic materials comprising primarily silk fibroin is the use of a naturally based material, produced by green chemistry, more biodegradable and alleviating the impact of microplastics on health and environment. In accordance with the present disclosure, it has been found that accurate and custom refractive index change pattern corrections can be advantageously written in this type of ophthalmic material.

[0057] For corneal inlays, using a refractive (optical) approach including writing refractive index change patterns, and not purely a mechanical approach such as forming a "bump," may be particularly advantageous. Figure 1A shows a current approach using a prolate-shaped inserted object 101 in the cornea 102 causing a "bump" 103 in the corneal surface, thereby providing increased refractive optical power in the central zone. In Figure 1B a "pocket" 104 is cut into the corneal tissue using conventional cornea cutting laser techniques. A nominally flat or slightly curved piece of a silk bio-compatible material, such as a silk-hydrogel composite material 105 in one embodiment, is first treated by laser scanning to produce the desired refractive correction using a LIRIC technique as described herein (see also Wayne H. Knox, "Inventing a new way to see clearly," Technology & Innovation, Volume 20, Number 4, August 2019, pp. 385-398(14), Publisher: National Academy of Inventors; Gustavo A. Gandara-Montano, L. Zheleznyak, and Wayne H. Knox, "Optical quality of hydrogel ophthalmic devices created with femtosecond laser induced refractive index modification," Optical Materials Express, Vol. 8, No. 2 | 1 Feb 2018 | Optical Materials Express 295 (2018); Ruiting Huang and Wayne H. Knox, "Quantitative photochemical scaling model for femtosecond laser micromachining of ophthalmic hydrogel polymers: effect of repetition rate and laser power in the four photon absorption limit," Vol. 9, No. 3 | 1 Mar 2019 | Optical Materials Express 1049; Ding et al. "Large refractive index change in silicone-based and non-silicone-based hydrogel polymers induced by femtosecond laser micro-machining," 27 November 2006 / Vol. 14, No. 24 / Optics Express 11901; Len Zheleznyak et al, "First-in-human laser-induced refractive index change (LIRIC) treatment of the cornea," Investigative Ophthalmology & Visual Science July 2019, Vol.60, 5079), and then inserted into the pocket incision created in the corneal tissue. As shown in Figure 1B, as an add power pattern is written directly into the corneal inlay, no significant bump needs to be produced in the cornea surface.

[0058] The use of LIRIC to define the refractive power should be more reproducible than relying on mechanical distortions of the cornea stroma to effect shape changes in the cornea surface. Figures 2A-2C (wherein a cornea flap 211 is cut in cornea 202 in Figure 2A, as in a first step of conventional LASIK; Silk optics layer 205 is placed over exposed stroma bed and the flap is re-set in Figure 2B; and LIRIC custom vision correction pattern is written into the Silk layer at a later time by exposure to laser 213 in Figure 2C) further show that the layer of silk material could be placed on top of an exposed stroma in a normal LASIK procedure, and then covered for later use in vision correction, without performing any LASIK ablation. The silk optics layer could provide a refractive index change profile that is more stable over time than when writing LIRIC directly into the cornea stroma (Len Zheleznyak et al, "First-in-human laser-induced refractive index change (LIRIC) treatment of the cornea," Investigative Ophthalmology & Visual Science July 2019, Vol.60, 5079).

[0059] Furthermore, Figures 3A-3C (wherein a cornea flap 311 is cut in cornea 302 in Figure 3A, as in a first step of conventional LASIK, and normal LASIK ablation procedure is performed on the exposed stroma bed to form a modified surface 314; Silk optics layer 305 is placed over the exposed stroma bed modified surface 314 and the flap is re-set in Figure 3B; and LIRIC custom vision correction pattern is written into the Silk layer at a later time by exposure to laser 313 in Figure 3C) show that the silk optics layer could be incorporated into a full LASIK procedure. After the flap is cut and the normal LASIK procedure has been done, the silk optics layer can be placed over the exposed LASIK modified cornea stroma and then the flap closed. Then, at any later date as desired, the LASIK treatment could be adjusted without having to re-lift the flap (which is not recommended) by simply writing the LIRIC refractive correction directly into the silk layer.

[0060] A similar approach can be applied on phakic or non-phakic IOLs where the lenses can be manufactured in a biocompatible material comprising primarily silk fibroin, and refractive index profiles can be written using the LIRIC procedure (either pre- or post-implantation).

EXAMPLE 1

[0061] LIRIC results have been obtained in a silk-hydrogel composite material comprising primarily silk fibroin. The silk hydrogel composite material was obtained by polymerizing 25 wt.% of HEMA and EGDMA monomers (in a proportion HEMA to EGDMA of 17:1) and 75wt.% of Silk fibroin, based on the total weight of monomers and silk fibroin as described in the examples of EP Appl. No. 23383047.0 filed October 11, 2023. The monomer mixture was prepared by stirring the monomers in liquid form, and adding a 0.6 wt.% of AIBN as polymerization initiator with respect to the total weight of HEMA and EGDMA. The AIBN is dissolved into the monomer mixture by using ultrasound to provide a polymerization mixture. A 3% silk fibroin solution in water was prepared. An appropriate weight of polymerization mixture including AIBN was added to the silk fibroin solution in order to have a 25% in weight of monomers with respect to the total weight of monomers and silk fibroin. The silk fibroin solution was stirred with the polymerization mixture at 700 RPM for 2 minutes. The obtained reaction mixture was cast in a petri dish, covered with a lid and polymerized at 60°C overnight.

[0062] Figure 4 shows the laser writing system that was used. A mode locked Ti:Sapphire laser 421 (Vitesse; Coherent Corporation, Santa Clara, CA, USA) emitting 800nm, ~100fs pulses at 80MHz was employed, where the 800nm beam was first frequency doubled to 400nm with a second harmonic generator 422. A variable neutral density filter 423 is introduced into the beam path to vary the writing power of the system. Using a 400 nm laser at 80 MHz repetition rate, we wrote a series of phase bars in a piece of silk-hydrogel composite 405 that was 100 microns thick, focusing the laser beam with objective 424 and scanning at a range of scan speeds and with a system effective NA of 0.4. The sample is mounted on to a three-dimensional x-y-z translation stage 425 (Aerotech Inc., Pittsburgh, PA, USA) to raster scan the focused 400nm beam inside of the sample. By attaching the sample to the stage and programming the stage to move in the horizontal plane, rectangular bars of uniform refractive index change are created.

[0063] Figures 5A and 5B shows a result obtained when writing phase bars of 50 microns width in the silk-hydrogel composite material at a scan speed of 15 mm/sec and average power of 39 mW. Figure 5A shows a Mach-Zehnder interference pattern caused by transmission through a phase bar, and Figure 5B shows the retrieved phase shift measured at 633 nm, corresponding to a phase shift of -0.89 waves, indicating that phase shifts of almost one wave are obtainable at relatively low average powers and reasonable scan speeds.

[0064] Figure 6 shows a further bright field photo of three phase bars 631, 631, 633 written in the silk-hydrogel material at 5, 10 and 15 mm/sec scan speeds, respectively, with a system effective NA of 0.4. The phase bars are clear and transparent, indicating pure phase shift has been written in the material.

EXAMPLE 2

[0065] A second femtosecond micromachining system was used to demonstrate the application of silk fibroin as a contact lens material for large scale production of refractive correctors (setup shown in Fig. 7). The system includes a KM Labs Y-Fi (Ytterbium fiber) laser 721, which delivers 1035nm, 120fs pulses at 8.3MHz. The Y-fi laser contains an internal second harmonic generator that frequency doubles the pulses to produce 517 nm laser beam. A combination of low GDD mirrors and a silver mirror is used to steer the 517 nm beam from the source through a microscope objective 724 (Olympus UPLFLN 40X 0.75NA) that is connected to a vertical stage 726 (Newport GTS30V) to adjust Z-height determined by a back reflection monitor 728. The silk fibroin sample is mounted to a 2D translation stage 727 (Aerotech PRO115LM) and scan speeds of 20 to 200mm/s was used at an average power of 507mW. Multiple phase bars were also written with a set scan speed of 50mm/s and average power varying from 370-980mW in four identically produced wet silk fibroin samples to determine LIRIC scalability with writing power. The samples were then autoclaved in saline solution at 121°C to allow the written regions to attain maximum phase shift.

[0066] Figs. 8A and 8B illustrate differential interference contrast in transmision mode (TDIC) and bright field microscopy in transmision mode (TBF) images for pairs of 30um wide phase bars written with 517nm 8.3MHz 50mm/s effective NA 0.6 at different average powers of 451mW and 502mW in wet silk fibroin material with 50um scale bars. Under TBF (Fig. 8B), transparent phase bars are observed while the corresponding TDIC images (Fig. 8A) showed relief at the edges of the phase bars indicating the presence of phase objects without damage. It was not possible to focus the phase bars within the field of view of the microscope, as shown in Figure 8B, indicating that the depth along which the phase bars are written was not constant, which could be due to a nonuniform thickness of the silk hydrogel. To obtain interferograms, the phase bars were then imaged under a Mach Zehnder interferometer and the corresponding phase shift was calculated. A plot of the magnitude of phase shift induced versus the average writing power is shown in Figure 9A. The error bars in the plot relate to nonuniformity of phase change measured between different samples and not within the same phase bar written in an individual sample. Fig. 9B is a differential interference contrast in reflection mode (RDIC) image for phase bars written at average powers of 449 mW, 502 mW, 546 mW, and 608 mW, illustrating the onset of damage at an average power of 608mW. Phase bars written with powers equal to and above 608 mW showed dark regions and portions missing, indicating the onset of damage. Also, regions written above 608mW, which exhibited smooth phase bars under differential interference contrast in reflection mode (RDIC), appeared with distorted edges under the interferometer making it difficult to construct phase maps.

[0067] A similar experiment was carried out with the average power set at 507mW, and the scan speed was varied from 20mm/s to 200mm/s. Figs 10A-B show bright field microscopy in reflection mode (RBF) 300x (Fig. 10A) and RDIC 300x (Fig. 10B) images of phase bars written at 80, 60, 40, and 20mm/s (left to right) at an average power of 507mW. Figs 10C shows a diagram of interferogram pattern of a phase bar and Fig. 10D shows the corresponding wavefront map of the phase bar written with λ =517nm, 40mm/s, 507mW in hydrated silk material autoclaved in saline solution. The phase bars written at speeds above 80mm/s were very faint while Figs 10A-10D demonstrate that phase bars written with scan speeds below 80mm/s were prominent under the RBF and RDIC microscope. The onset of damage was noticed at 20mm/s. An average phase shift of -0.4 ± 0.03 waves is observed at writing wavelength of 517nm, scan speed 40mm/s and average power 507mW.

[0068] In further experiments, the sign of the phase change written in the silk fibroin materials as described above was determined to be negative by a wedge experiment similar to the technique described in G. A. Gandara-Montano, et a., "Femtosecond laser writing of freeform gradient index microlenses in hydrogel-based contact lenses," Opt. Mater. Express, OME 5(10), 2257–2271 (2015).

[0069] The foregoing description of the use of LIRIC laser treatment of bio-compatible silk optical materials is not meant to be limiting, as there will be further applications of this technology. The simultaneous availability of customized refractive index corrections in a bio-compatible material solves many problems in ophthalmology, and in other fields as well.

[0070] In particular embodiments, hydrogel materials comprising primarily silk fibroin may be LIRIC processed to form refractive index change patterns therein while in either a hydrated or a non-hydrate form, and may be written in before or after insertion in an eye. Such versatility allows for design of a variety of techniques for forming desired refractive correction patterns during manufacturing or otherwise prior to implantation in a patient, or in situ after implantation to achieve further desired performance in a patient.

[0071] The term "hydrogel" as employed in the present disclosure refers to an optical, polymeric material that can absorb greater than 10% by weight water based on the total hydrated weight. In fact, many optical, hydrogel polymeric materials will be able to absorb a water content greater than 15% or greater than 20%. For example, in various embodiments, hydrogel polymeric materials may have a water content from 10% to 80%, or from 15% to 80%, or from 15% to 60%, or from 15% to 40% in their fully hydrated states. For use in an optical device, the polymeric hydrogel materials should be of sufficient optical clarity, and may have a relatively high refractive index of approximately 1.40 or greater, particularly 1.48 or greater.

[0072] Without exclusion as to any ophthalmic materials or material modifications, e.g., the inclusion of a photosensitizer, or laser parameters described herein, the foregoing disclosed techniques and apparatus can be used to modify the refractive properties, and thus, the dioptric power, of an ophthalmic material comprising primarily silk firoin as described herein, by creating (or machining) a refractive structure with a gradient index in one, two or three dimensions of the optical material, as more fully described in U.S. Publication Nos. 2012/0310340 and 2012/0310223, incorporated by reference herein. The gradient refractive structure can be formed by continuously scanning a continuous stream of femtosecond laser pulses having a controlled focal volume in and along at least one continuous segment (scan line) in the ophthalmic material while varying the scan speed and/or the average laser power, which creates a gradient refractive index in the ophthalmic material along the segment. Accordingly, rather than creating discrete, individual, or even grouped or clustered, adjoining segments of refractive structures with a constant change in the index of refraction in the material, a gradient refractive index may be created within the refractive structure, and thereby in the optical material, by continuously scanning a continuous stream of pulses. As described in greater detail in U.S. Publication No. 2012/0310340, since the refractive modification in the material arises from a multiphoton absorption process, a well-controlled focal volume corrected for spherical (and other) aberrations will produce a segment having consistent and, if desired, constant depth over the length of the scan. As further noted, when a tightly focused laser beam consisting of femtosecond pulses at high repetition rate impinges on a material that is nominally transparent at the incident laser wavelength, there is little if any effect on the material away from the focal region. In the focal region, however, the intensity can exceed one terawatt per square centimeter, and the possibility of absorbing two or more photons simultaneously can become significant. In particular, the amount of two-photon absorption can be adjusted by doping or otherwise including in the irradiated material with selected chromophores that exhibit large two-photon absorption cross-section at the proper wavelength (e.g., between 750 nm and 1100 nm), which can significantly increase the scanning speed as already described. Also, multiple segments can be written into the material in a layer using different scan speeds and/or different average laser power levels for various segments to create a gradient index profile across the layer, i.e., transverse to the scan direction. Further, multiple, spaced gradient index (GRIN) layers can be written into the material along the z-direction (i.e., generally the light propagation direction through the material) to provide a desired refractive change in the material that provides a significant added dioptric power or that otherwise corrects for some, most, or all higher order aberrations of a patient's eye. Such abilities to write continuously varying gradient index layers are particularly advantageous in forming refractive correctors having wavefront cross-section profiles. For ophthalmic applications, it is of particular interest that GRIN refractive structures are low scattering (as discussed above) and are of high optical quality.

[0073] In particular contemplated embodiments of the present disclosure, GRIN refractive structures in the form of Fresnel lens patterns may be LIRIC written in ophthalmic material comprising primarily silk fibroin.

[0074] The laser may generate light with a wavelength in the range from violet to near-infrared. In various aspects, the wavelength of the laser may be in the range, e.g., from 340 nm to 1500 nm, from 400 nm to 1200 nm, from 400 to 600, or from 650 nm to 1100 nm, including more specifically wavelengths near 400 nm, 517 nm, 800 nm, and 1035 nm. Example pulsewidths include femtosecond scale pulsewidths, and, in some examples, pulsewidths less than 350 fs. Example repetition rates include repetition rates in the range of 1-80 MHz. Example lens NA include NA's between 0.19 and 1.0. Any suitable scanning system may be utilized, including, without limitation, high speed XYZ translation stages, high speed galvanometer scanning systems, and shaker scanners (such as described in U.S. Patent Application Publication No. 2016/0144580 published May 26, 2016 to Wayne H,. Knox et al.). In some instances, the scanning speed may be in the range of 1 mm/sec to 10 meters/sec or even higher.

[0075] The laser scanning system may deliver short laser pulses of sufficient energy (e.g. above a minimal threshold but below a damage threshold) and at sufficient scan speeds (e.g. above a damage threshold but below an upper speed threshold) to cause a nonlinear absorption of photons (typically multi-photon absorption), leading to a change in the refractive index of the material at the focus point. The damage threshold may reflect a threshold in which a degradation in optical quality of the device is detectable. Moreover, the region of the material just outside the focal region is minimally affected by the laser light. Accordingly, select regions of an ophthalmic material comprising primarily silk fibroin material can be modified with a laser resulting in a change in the refractive index in the exposed regions. The irradiated regions may exhibit no significant differences in the Raman spectrum with respect to the non-irradiated regions. Also, the irradiated regions may exhibit little or no scattering loss, which means that the structures formed in the irradiated regions are not clearly visible under appropriate magnification without contrast enhancement.

[0076] The described writing systems may be utilized to create lenses or other optical constructs in the interior of the material to change their optical properties. Depending on the phase shift required, the lens or other optical construct can be written into the material in a single layer or in multiple layers. U.S. Patent 8,932,352, issued January 13, 2015 to Wayne H. Knox et al. for an "Optical Material and Method for Modifying the Refractive Index" and U.S. Patent 9,144,491, issued September 29, 2015 to Wayne H. Knox et al. for a "Method for Modifying the Refractive Index of an Optical Material," describe additional examples of gratings and other optical constructs that may be written into materials.

[0077] A first step to determining material characteristics for planning desired writing parameters in an ophthalmic material comprising primarily silk fibroin in accordance with the present disclosure may be to measure written phase shifts obtainable in the material of interest as a function of, for example, average power and scan speed. Phase vs. power can be plotted on log-log scales to determine slope of nonlinear processes in small signal regime (below saturation). The determined slope may be indicative of the applicable photochemical model for the material of interest (e.g. a slope close to 2 may be indicative of a two photon model, a slope close to 4 may be indicative of a four photon model, etc.). The applicable photochemical models (e.g. the two and/or four photon regime models) may be fit to the data, and a maximum phase shift just below the damage threshold may be identified. This information may be subsequently used to establish a range of writing powers at desired scan speeds, to enable controlling a laser power and scan rate for maintaining an energy profile in the ophthalmic material within the focus volume above a nonlinear absorption threshold of the ophthalmic material, and below a material damage breakdown threshold of the ophthalmic material which would result in ablation or observable burning or carbonization of the ophthalmic material. It is noted that, while the best results for at least some systems and methods are obtained when the one-photon absorption is minimized, a small amount of one-photon absorption may be tolerable even in those instances.

[0078] The disclosures of all cited patent, patent application, and further publications cited herein are incorporated by reference herein.

Claims:

1. A method of forming a silk fibroin containing optical device with a modified refractive index pattern provided therein comprising:

providing an optical device comprising an ophthalmic material made primarily of silk fibroin;

forming at least one laser-modified pattern within the optical device by exposing regions of the ophthalmic material to light pulses from a laser to cause changes in the ophthalmic material in the exposed regions sufficient to cause a change in refractive index of the exposed regions relative to the refractive index of the ophthalmic material in non-exposed regions.

2. The method of claim 1 wherein the laser exposure is performed by scanning focused pulses from the laser along regions of the ophthalmic material, while controlling a laser power and scan rate for maintaining an energy profile in the ophthalmic material within the focus volume above a nonlinear absorption threshold of the ophthalmic material, and below a material damage breakdown threshold of the ophthalmic material which would result in ablation or observable burning or carbonization of the ophthalmic material.

3. The method of claim 1 or 2 wherein the ophthalmic material comprises a silk fibroin hydrogel material.

4. The method of claim 3, wherein the silk fibroin hydrogel material is obtainable by polymerizing one or more hydrophilic monomers and silk fibroin in the presence of a copolymerization initiator.

5. The method of claim 4, wherein the silk fibroin hydrogel material is obtainable by polymerizing hydroxy ethyl methacrylate (HEMA), ethylene glycol dimethacrylate (EGDMA), and silk fibroin in the presence of a copolymerization initiator.

6. The method of any of the preceding claims, wherein the optical device is in the form of a corneal inlay, and further comprising implanting the corneal inlay in the cornea of an eye.

7. The method of claim 6, wherein the laser exposure is performed prior to implanting the corneal inlay in the cornea of a patient to provide a desired refractive correction.

8. The method of claim 7, wherein the laser exposure is performed to provide a desired add power for correcting presbyopia.

9. The method of claim 6, wherein the laser exposure is performed after implanting the corneal inlay in the cornea of a patient to provide a desired refractive correction.

10. The method of claim 9, wherein the laser exposure is performed to provide a desired add power for correcting presbyopia.

11. The method of any of the preceding claims, wherein the laser-modified pattern formed in the ophthalmic material forms gradient index refractive structures in the form of a Fresnel lens pattern.

12. An optical device comprising an ophthalmic material made primarily of silk fibroin having at least one laser-modified refractive index change pattern formed there within, made according to the method of any of claims 1-11.

13. An optical device according to claim 12, comprising a contact lens, a corneal inlay, a phakic IOL, or a non-phakic IOL.

14. An optical device according to claim 12, comprising a contact lens.

15. An optical device according to claim 12, comprising a corneal inlay.

16. An optical device according to claim 12, comprising a phakic or a non-phakic IOL.

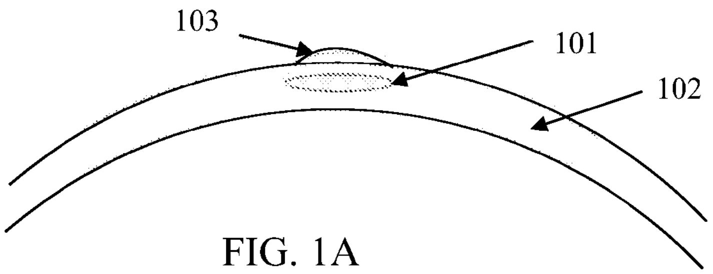


FIG. 1A

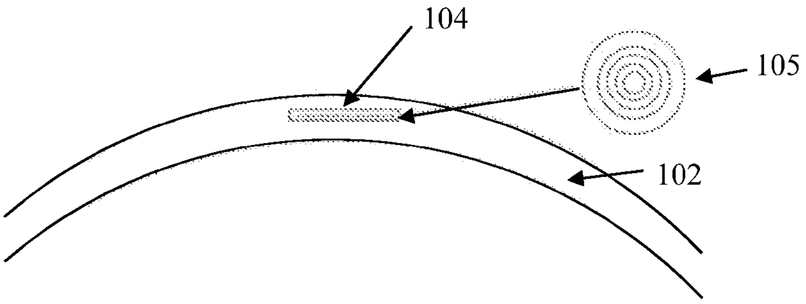


FIG. 1B

FIG. 2A

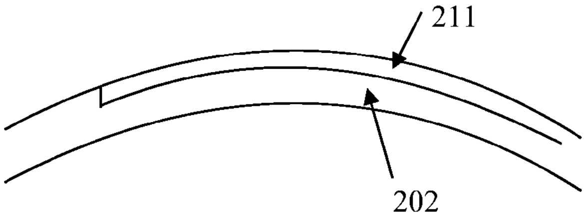


FIG. 2B

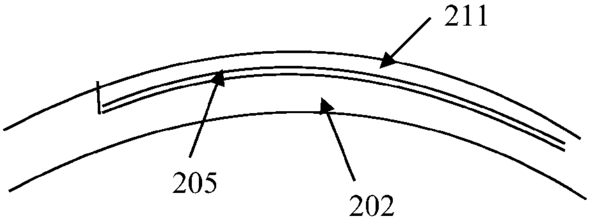


FIG. 2C

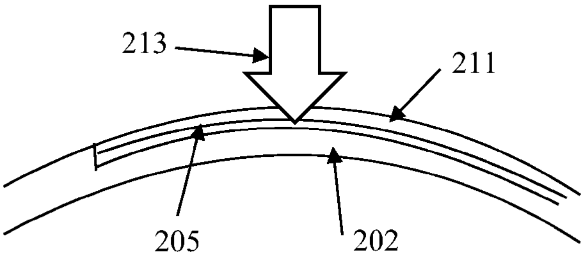


FIG. 3A

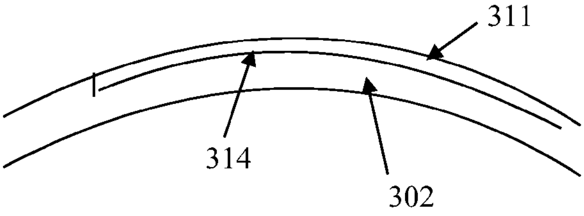


FIG. 3B

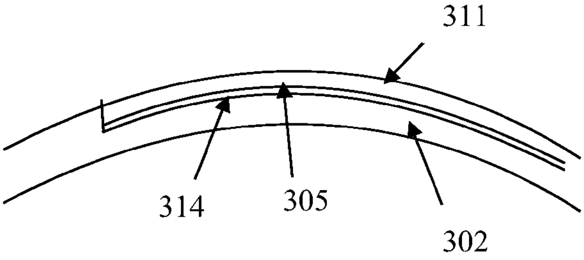
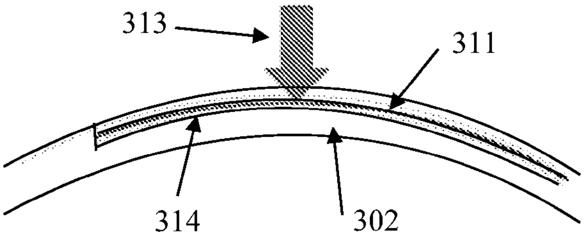


FIG. 3C



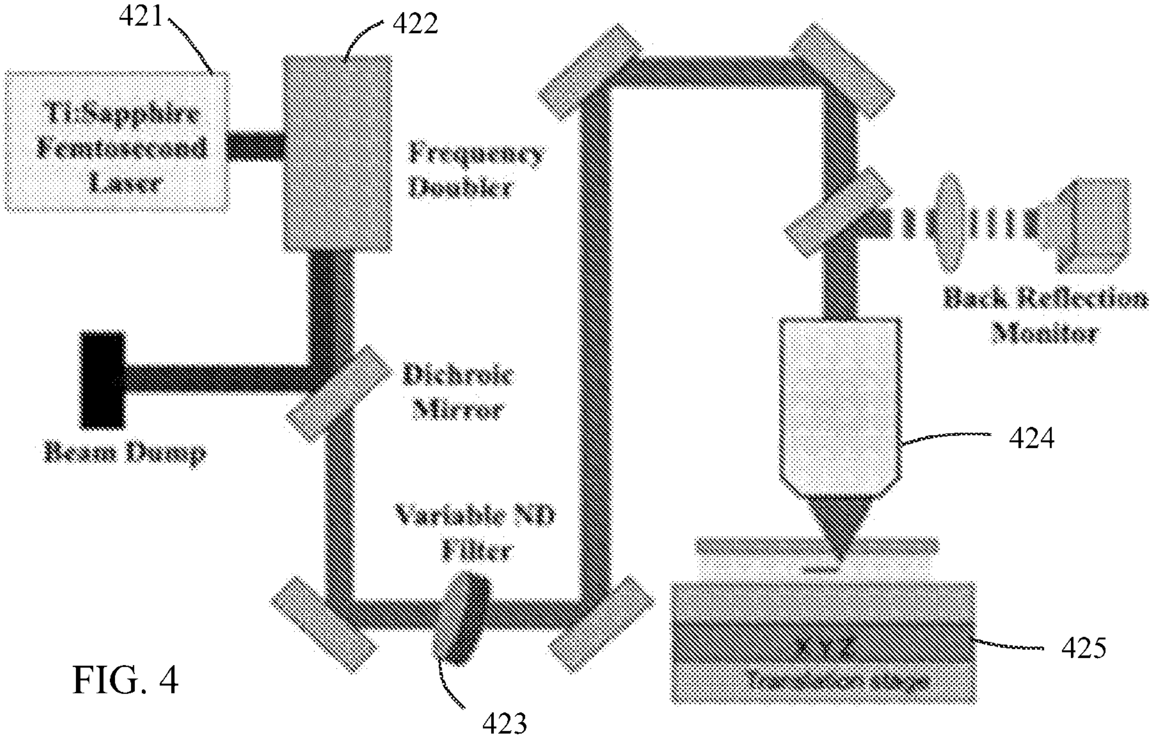


FIG. 4

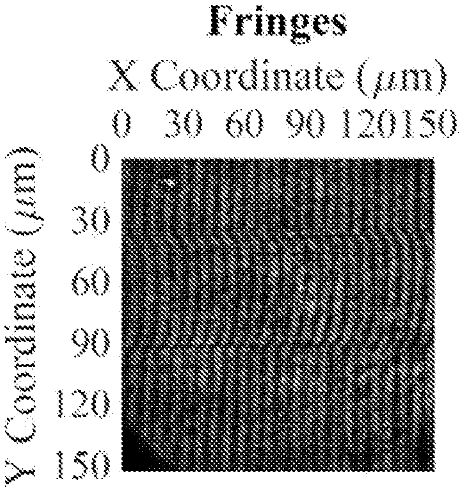


FIG. 5A

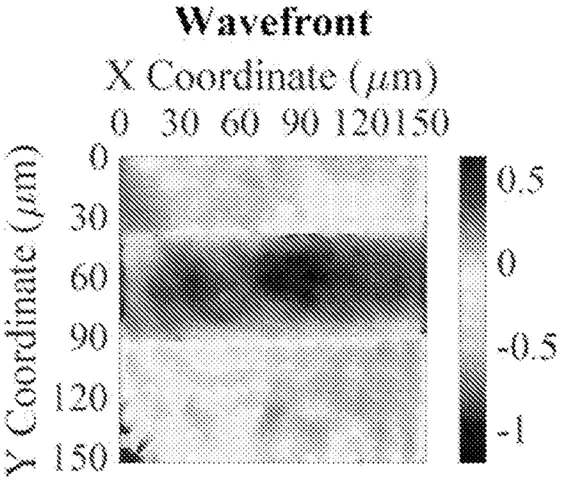


FIG. 5B

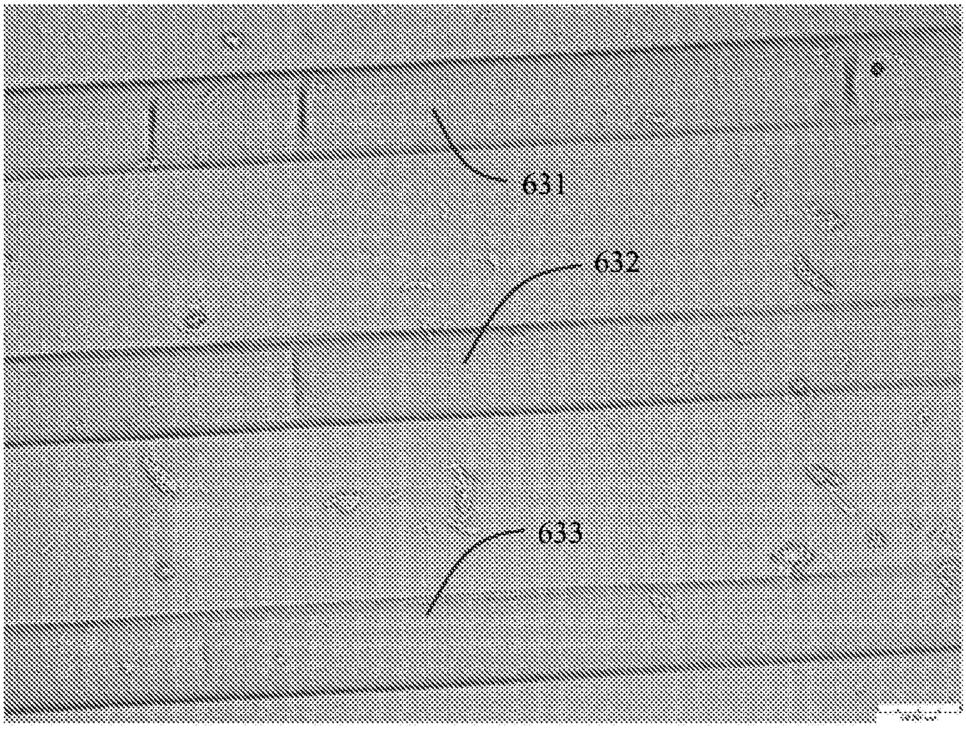

631
632
633

FIG. 6

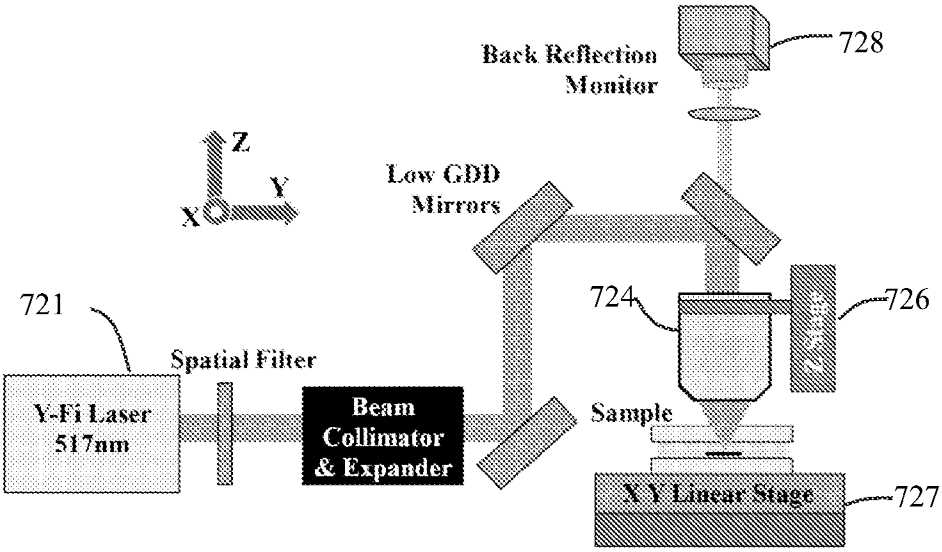

728
Back Reflection Monitor
Z
Y
X
Low GDD Mirrors
724
726
Z Stage
721
Spatial Filter
Y-Fi Laser 517nm
Beam Collimator & Expander
Sample
X Y Linear Stage
727

FIG. 7

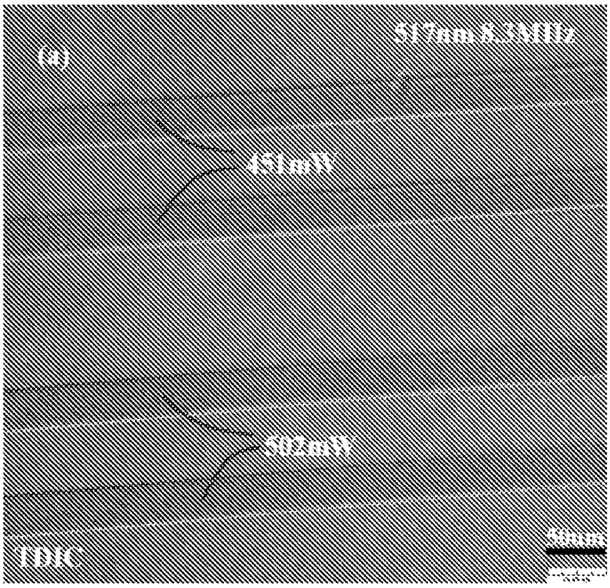


FIG. 8A

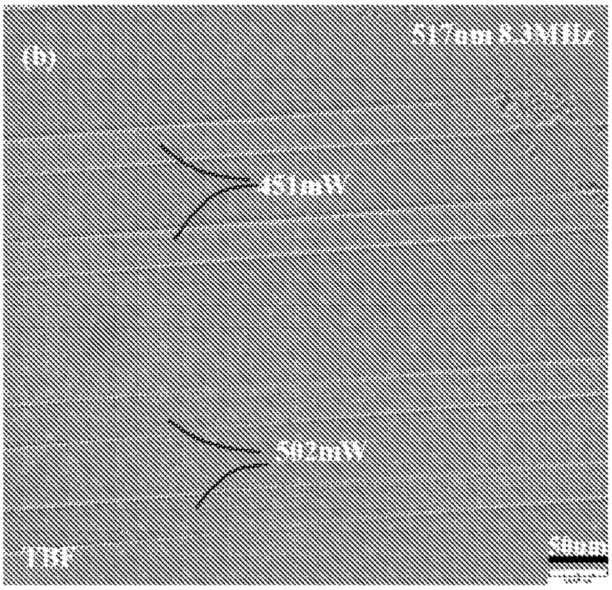


FIG. 8B

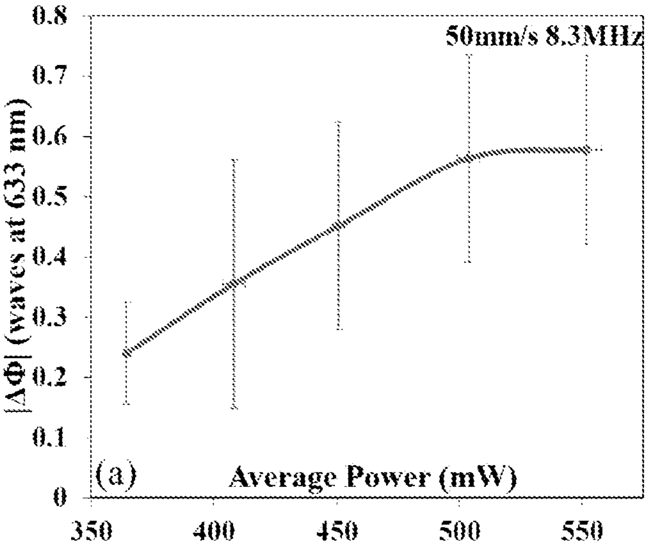


FIG. 9A

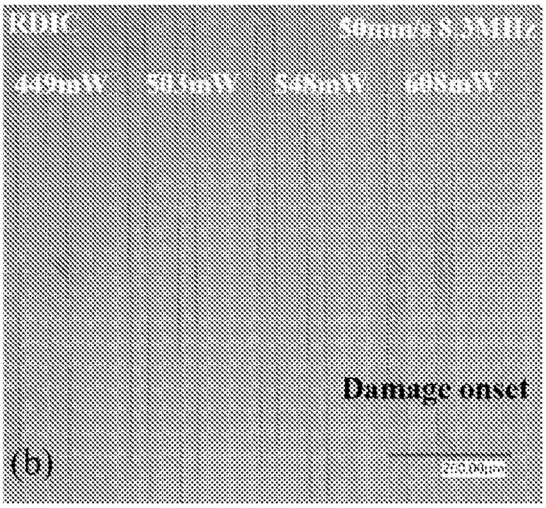


FIG. 9B

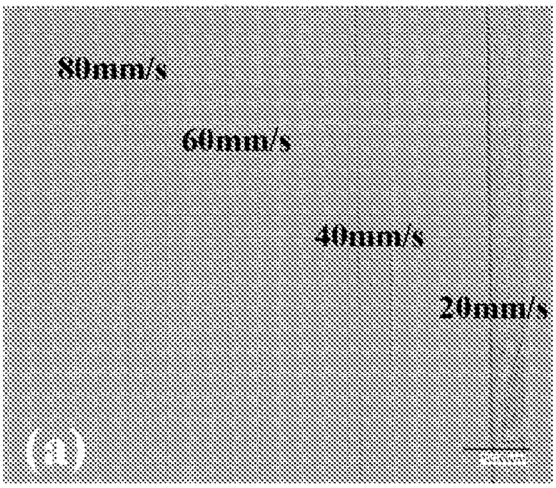


FIG. 10A

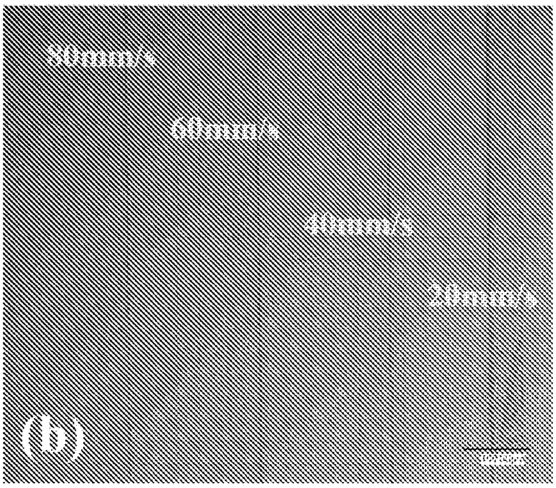


FIG. 10B

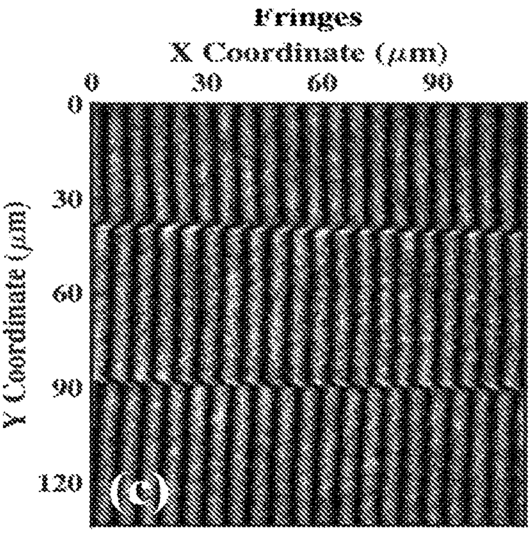


FIG. 10C

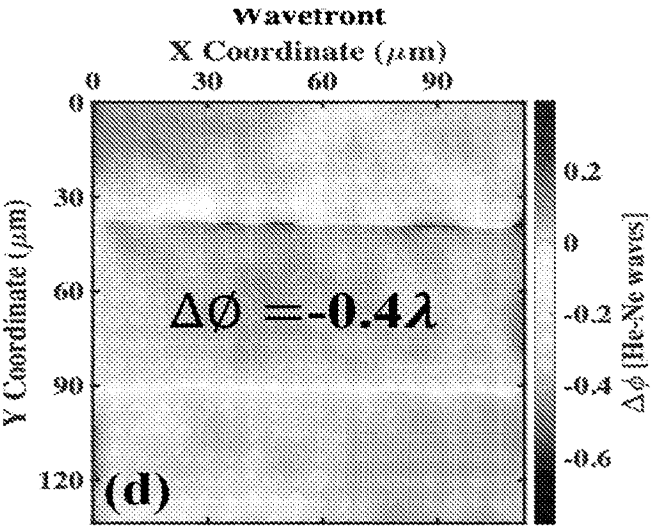


FIG. 10D

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/051757

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61F2/16 A61L27/52 G02B1/04 A61F9/008
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61F G02B A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SANTOS MOLÍRIA V ET AL: "Femtosecond direct laser writing of silk fibroin optical waveguides", JOURNAL OF MATERIALS SCIENCE: MATERIALS IN ELECTRONICS, CHAPMAN AND HALL, LONDON, GB, vol. 30, no. 18, 30 April 2019 (2019-04-30), pages 16843-16848, XP036894946, ISSN: 0957-4522, DOI: 10.1007/S10854-019-01406-W [retrieved on 2019-04-30]	1
Y	paragraphs [0002], [0018], [0046], [0066] -----	2-5, 11-16
Y	US 2016/296662 A1 (STOY VLADIMIR [CZ] ET AL) 13 October 2016 (2016-10-13) paragraph [0066] ----- -/--	2,11-16

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 18 December 2024	Date of mailing of the international search report 07/01/2025
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Farizon, Pascal

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/051757

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2015/048527 A1 (UNIV TUFTS [US]) 2 April 2015 (2015-04-02) paragraphs [0024], [0223] -----	3-5
A	CAMPAIGN SARA M G ET AL: "Increase in efficacy of near-infrared laser induced refractive index change (LIRIC) in corneal tissue with sodium fluorescein and riboflavin: comparison of two repetition rates", SPIE PROCEEDINGS; [PROCEEDINGS OF SPIE ISSN 0277-786X], SPIE, US, vol. 11270, 2 March 2020 (2020-03-02), pages 1127005-1127005, XP060129868, DOI: 10.1117/12.2546418 ISBN: 978-1-5106-3673-6 abstract -----	1-5, 11-16
A	US 2018/243082 A1 (ZHELEZNYAK LEONARD [US] ET AL) 30 August 2018 (2018-08-30) paragraphs [0005], [0063], [0173] -----	1-5, 11-16

1

International application No.
PCT/US2024/051757

INTERNATIONAL SEARCH REPORT

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 6-10
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2024/051757

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2016296662 A1	13-10-2016	US 2016296662 A1	13-10-2016
		US 2020038549 A1	06-02-2020
WO 2015048527 A1	02-04-2015	US 2020165306 A1	28-05-2020
		US 2021002335 A1	07-01-2021
		WO 2015048527 A1	02-04-2015
US 2018243082 A1	30-08-2018	US 2018243082 A1	30-08-2018
		US 2021177576 A1	17-06-2021
		US 2021177577 A1	17-06-2021
		US 2021177578 A1	17-06-2021
		US 2021177579 A1	17-06-2021
		US 2023157812 A1	25-05-2023

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 6-10

The subject-matter of claim 6 (and consequently dependent claims 7-10), is directed to a method for modifying the refractive index of a corneal inlay. The method comprises the step of implanting the corneal inlay in the cornea of an eye . The International preliminary searching authority is not required to establish an opinion with regard to novelty, inventive step and industrial applicability on methods for treatment of the human body by surgery (Rule 39.1(iv) PCT).