US 20030028225A1

(19) **United States**

(12) **Patent Application Publication**

(10) **Pub. No.: US 2003/0028225 A1**

(43) **Pub. Date: Feb. 6, 2003**

Chow et al.

(54) **METHODS FOR IMPROVING DAMAGED RETINAL CELL FUNCTION USING PHYSICAL AND/OR MECHANICAL STIMULATION**

(76) Inventors: **Alan Y. Chow**, Wheaton, IL (US); **Vincent Y. Chow**, Hanover Park, IL (US)

Correspondence Address:
BRINKS HOFER GILSON & LIONE
P.O. BOX 10395
CHICAGO, IL 60611 (US)

(21) Appl. No.: **10/186,295**

(22) Filed: **Jun. 28, 2002**

Related U.S. Application Data

(63) Continuation-in-part of application No. 10/056,793, filed on Jan. 23, 2002.

(60) Provisional application No. 60/301,877, filed on Jun. 29, 2001.

Publication Classification

(51) **Int. Cl.**[7] **A61N 1/32**

(52) **U.S. Cl.** **607/54**

(57) **ABSTRACT**

Methods of using physical stimulation by itself or in conjunction with growth factors to treat and prevent visual loss due to choroidal, retinal pigment epithelial and/or neuroretinal cell degeneration and dysfunction are presented.

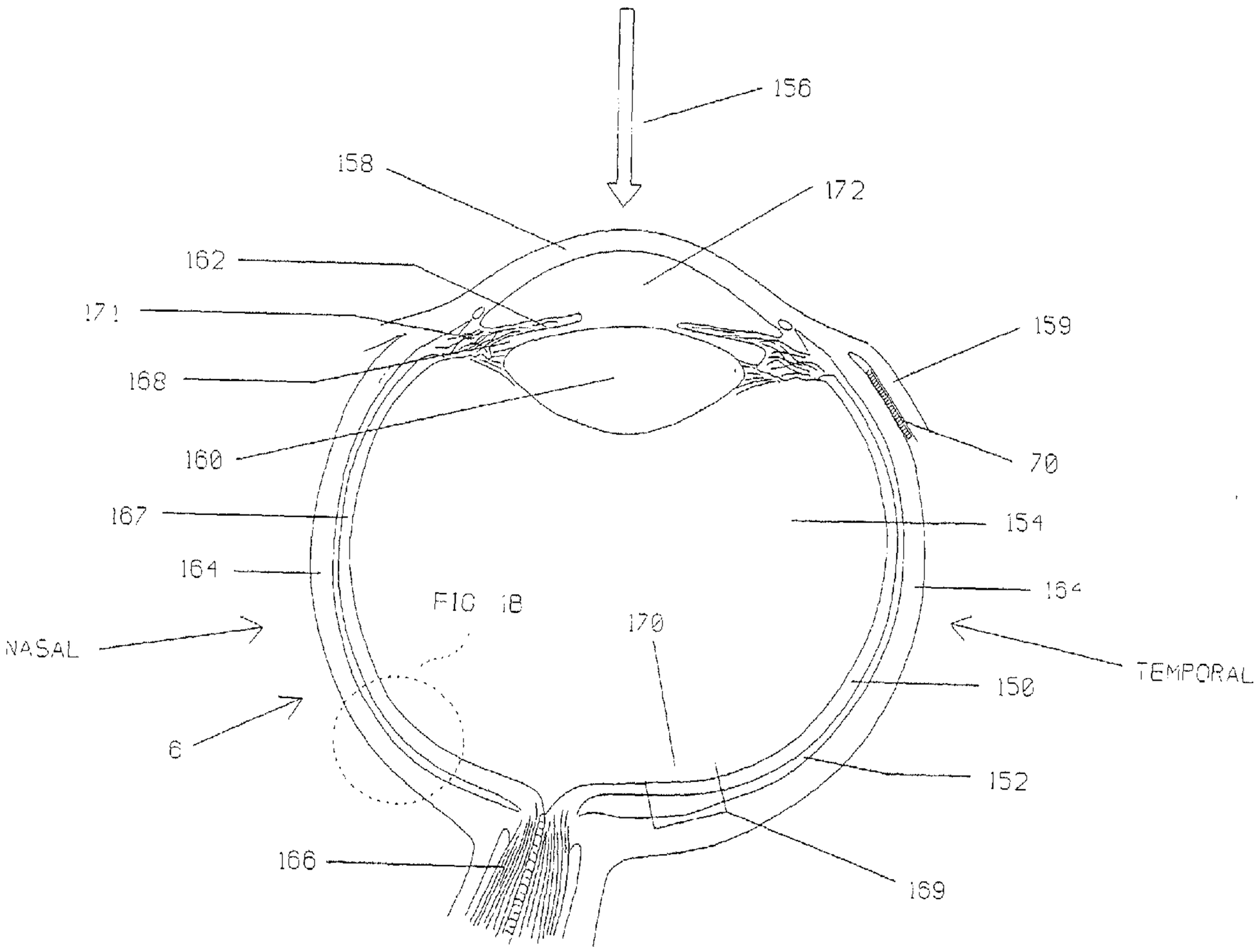


FIG 18

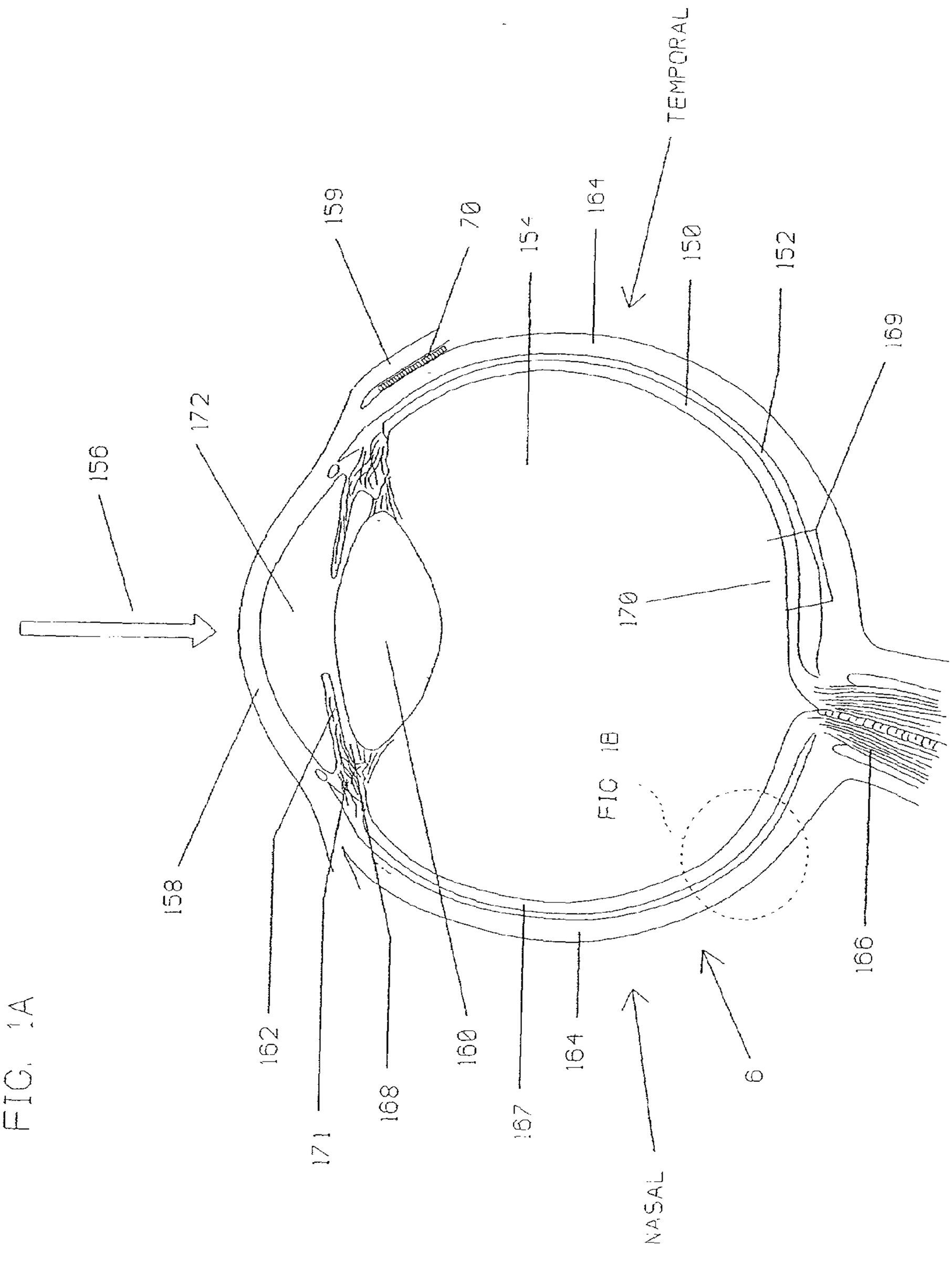

TEMPORAL
159
70
154
164
150
152
169
156
172
170
158
162
171
168
160
167
164
NASAL
6
166

FIG. 1A

FIG 1B

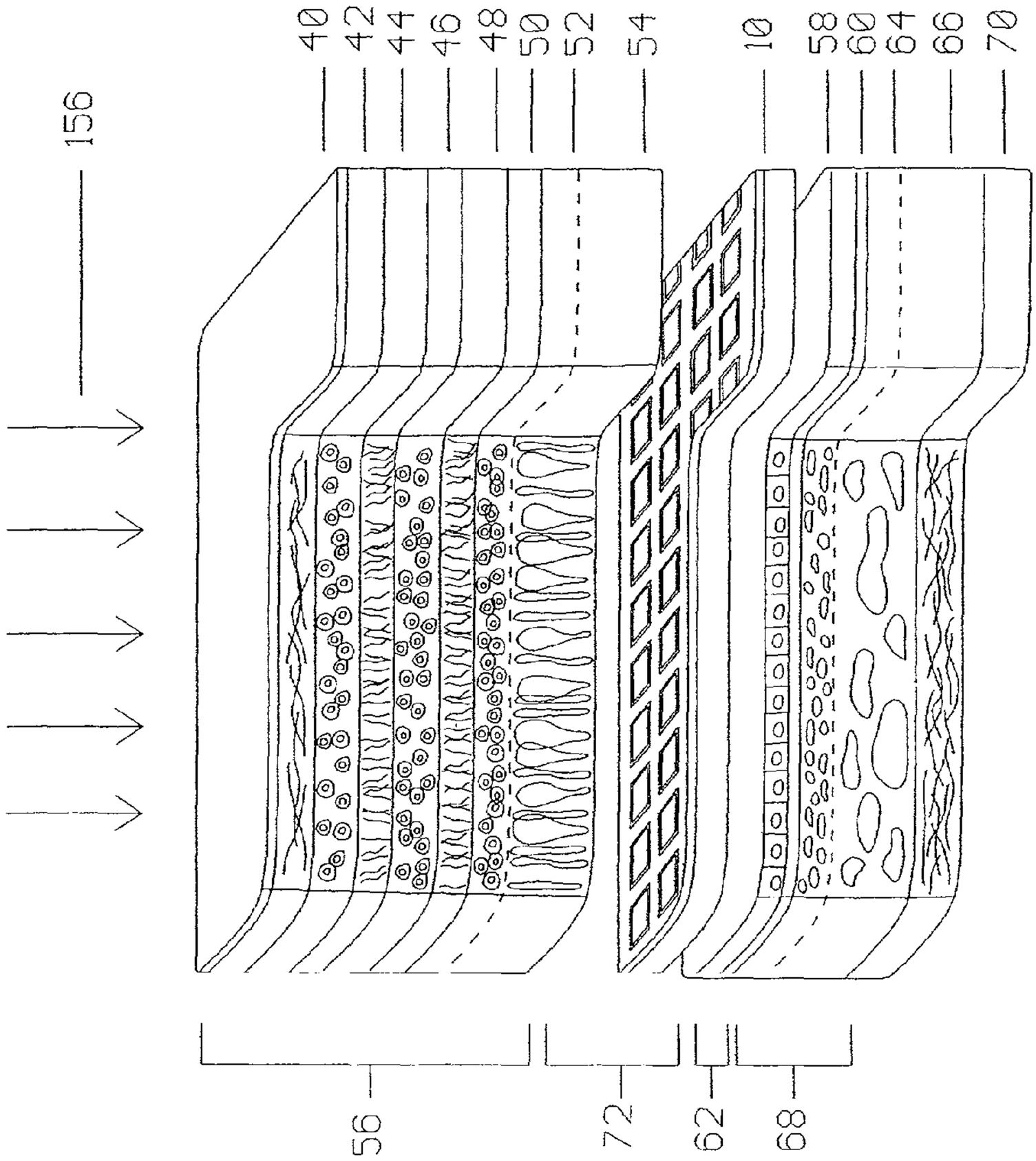


FIG. 1B

FIG. 2

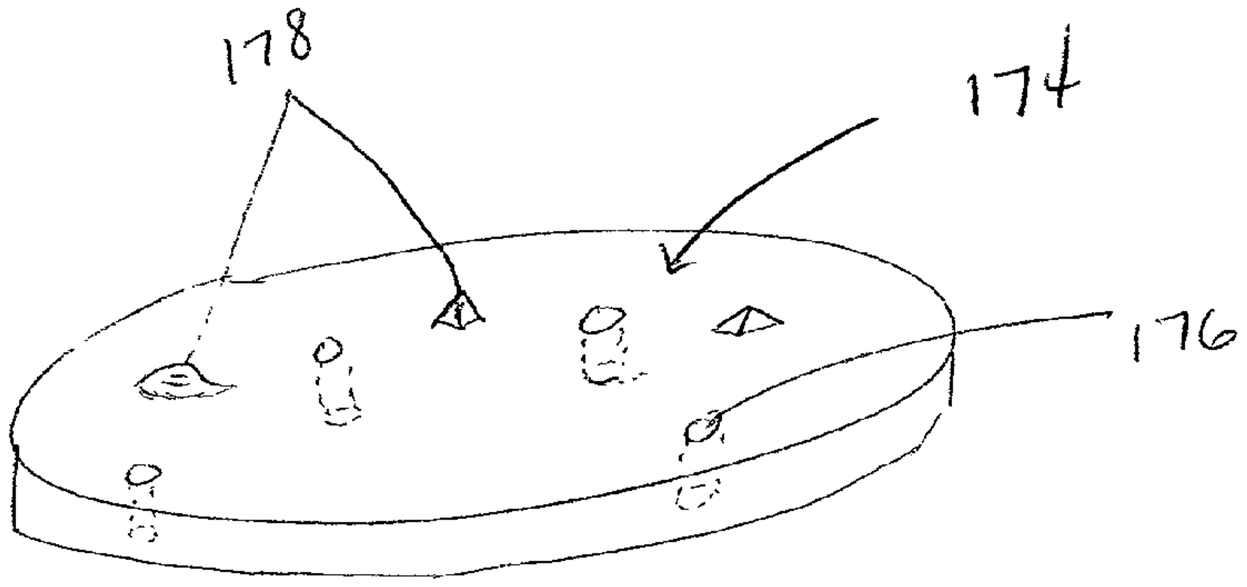


FIG. 3

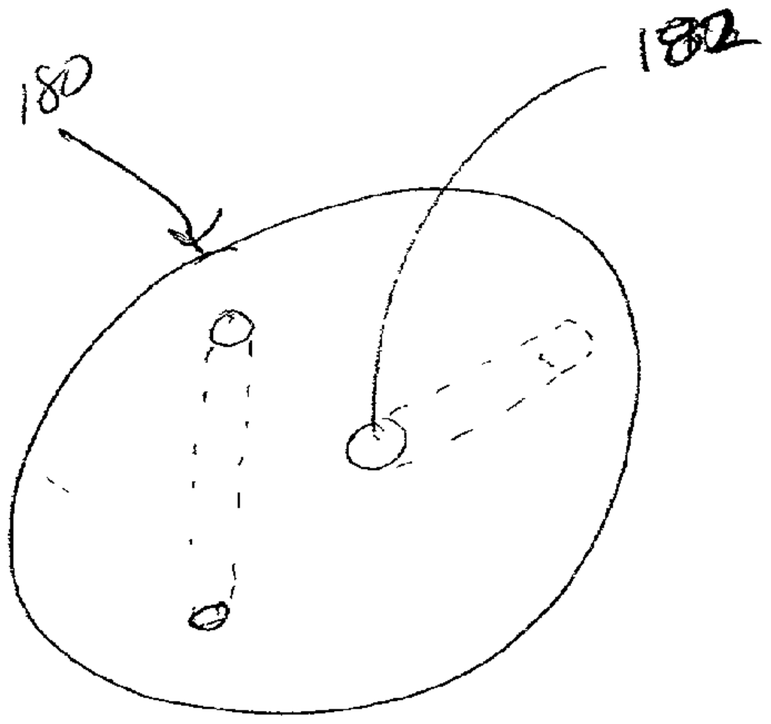


FIG. 4

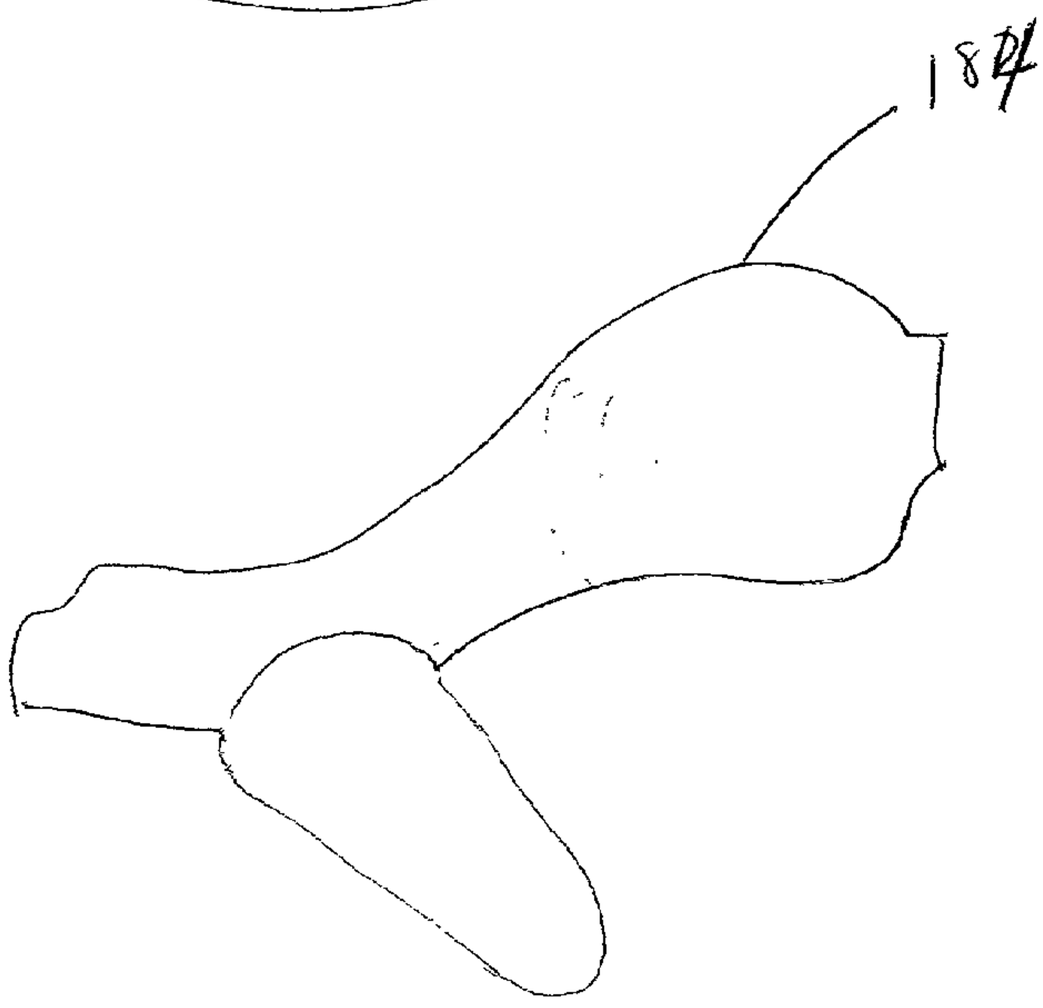


FIG. 5

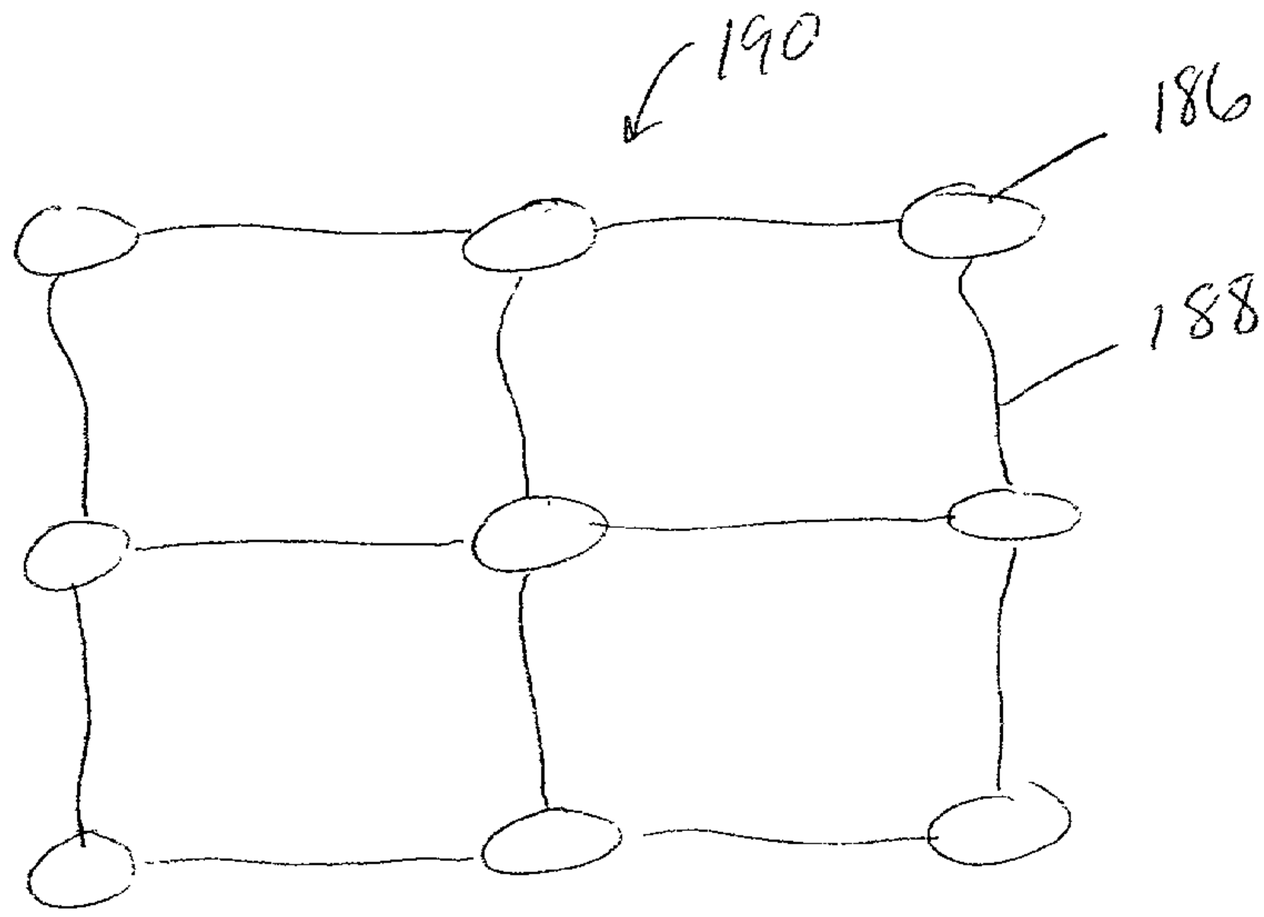
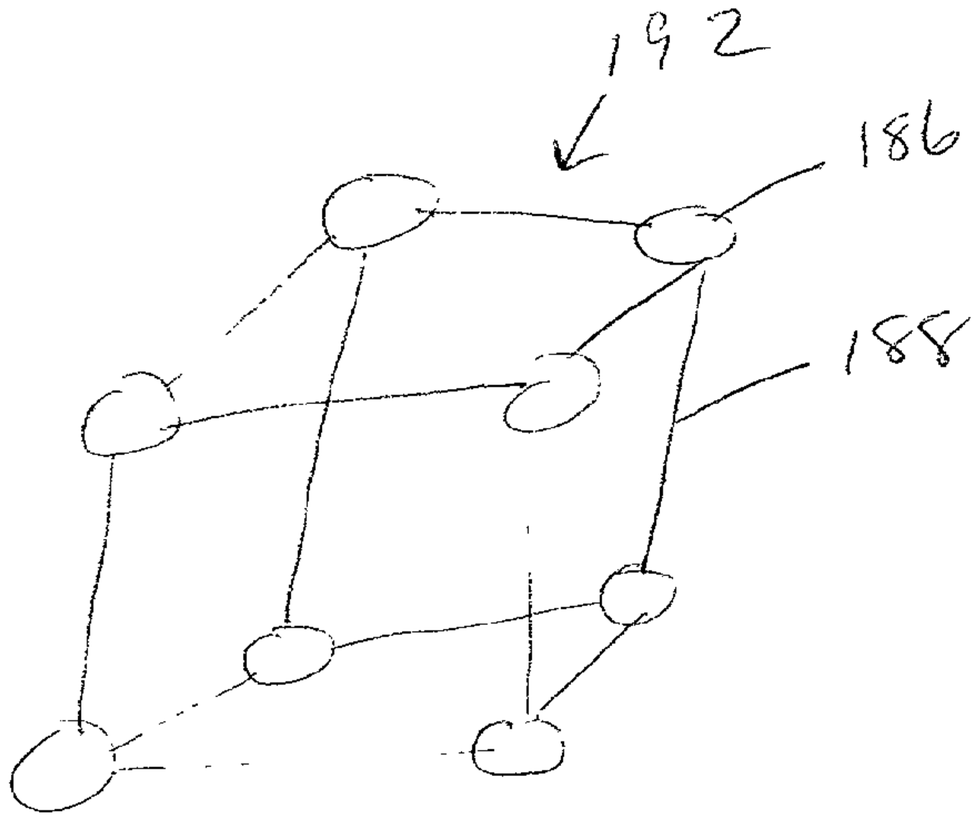


FIG. 6



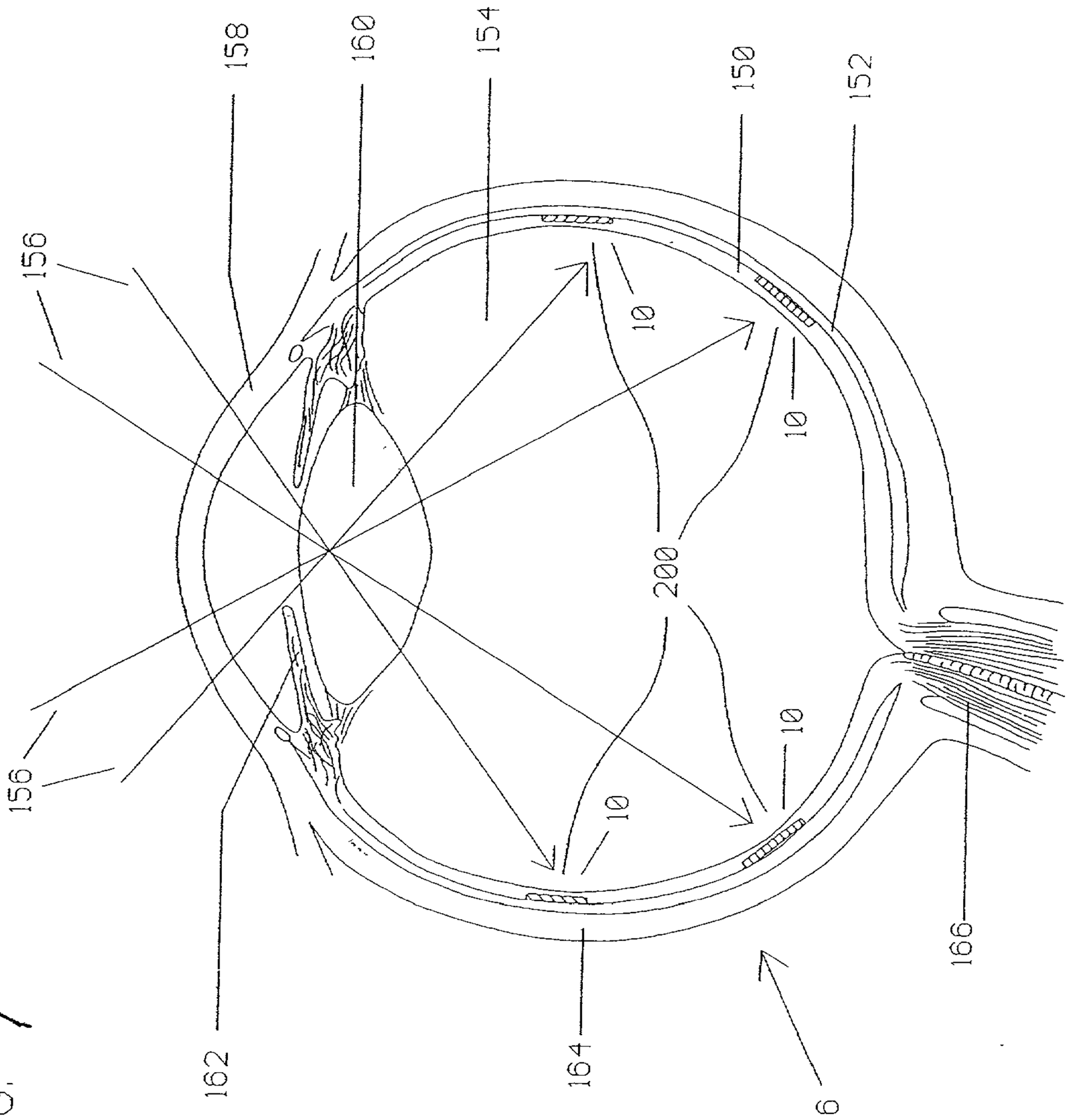


FIG. 7

METHODS FOR IMPROVING DAMAGED RETINAL CELL FUNCTION USING PHYSICAL AND/OR MECHANICAL STIMULATION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of non-provisional application serial No.10/056,793, filed Jan. 23, 2002, which claims the benefit of provisional application serial no. 60/301,877, filed Jun. 29, 2001, and both of the aforementioned applications are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present invention is directed to generally to improving biological cell function and more specifically to improving retinal cell visual function in damaged and/or degenerated retinas and also to protecting retinal cells from degeneration.

BACKGROUND

[0003] Certain biological chemical compounds such as nerve growth factors (NGF), neurotropins, brain-derived neurotrophic factors (BNDF), fibroblastic growth factor (FGF), glial cell line-derived neurotrophic factors (BDNF), and numerous other similar biological chemical compounds, all collectively known as survival-type factors can slow down the process of cellular degeneration in a number of biological degenerative diseases, specifically in retinal degenerative diseases and also promote cellular growth in other situations.

[0004] In studies, the application of survival-type factors was found to promote and maintain certain retinal cellular functions. For example, brain-derived neurotrophic factor (BDNF), neurotrophin-4 (NT-4), neurotrophin-5 (NT-5), fibroblastic growth factor (FGF) and glial cell line-derived neurotrophic factor (GDNF) have been shown to enhanced neurite outgrowth of retinal ganglion cells and to increase their survival in cell culture. GDNF has been shown to preserve rod photoreceptors in the rd/rd mouse, an animal model of retinal degeneration. Nerve growth factor (NGF) injected into the intra-ocular area of the C3H mouse, also a model of retinal degeneration, results in a significant increase of surviving photoreceptor cells compared to controls (Bosco and Linden, 1999; Caleo et al., 1999; Carmignoto et al., 1989; Cui et al., 1998; Frasson et al., 1999; Lambiase and Aloe, 1996; Reh et al., 1996).

[0005] However, while many prostheses are known that attempt to restore vision by using photoactive properties of semiconductors designed to mimic the electric charge that damaged retinal cells would otherwise generate, few devices or treatments are available that can slow, stop or reverse retinal degeneration.

SUMMARY

[0006] According to a first aspect of the invention, a method of improving visual function of a damaged retina in a human eye is disclosed. The method includes applying a chronic physical stimulation to the eye to improve or maintain visual function of the damaged retina, wherein applying chronic physical stimulation improves visual function of at least one structure of the damaged retina. In one embodiment the chronic physical stimulation is applied by a source of physical stimulation comprising at least one device in contact with any structure of the eye. The physical stimulation may be provided to at least one of the damaged retina and a structure of the eye. Also, the physical stimulation may be provided by one or more devices. The device or devices may be constructed of electrically inert, chemical or biological materials.

[0007] According to another aspect of the invention, a method of implanting a physically stimulating device in an eye of a patient having least one condition selected from the group consisting of outer neuroretina disease, choroidal disease and retinal epithelial disease is disclosed. The method includes implanting in a subretinal space in the eye of the patient at least one electrically inert device configured to contact a plurality of cells in the eye. The electrically inert device could also be implanted in other spaces of the eye of the patient, such as an epiretinal space, a subconjunctival space, a subscleral space, and/or in a subchoroidal space of the eye. In one embodiment, the device may be positioned in one of a peripheral or mid-peripheral region in the subretinal space, outside of a macula of the eye. In another embodiment, the electrically inert device may be implanted at a position in the subretinal space between an angle of about 50 to 800 off-axis from the macula, where the angle is defined by an intersection of an axis line extending from the macula to a central structure of the pupil and an off-axis line extending from the device to the central structure of the pupil.

[0008] In another aspect, the invention provides a use of a source of electrical stimulation for producing an implant for improving visual function that includes the perception of brightness in the presence of light, the perception of darkness in the absence of light, the perceptions of contrast, color, resolution, shape, motion, and visual field size of a damaged retina in a human eye by applying electrical stimulation to the damaged retina, eye or to both, wherein this electrical stimulation improves visual function of at least a portion of the damaged retina not in contact with the source of electrical stimulation.

[0009] In another aspect, the invention provides a use of a source of chronic or prolonged physical stimulation for producing an implant for treating primary and secondary visual degradation resulting from a damaged retina by applying physical stimulation to the eye with the damaged retina, wherein a portion of the damaged retina not in contact with the source of physical stimulation is treated. The damaged retina, for example, may comprise damaged photoreceptor cells, and such cells peripheral to the source of physical stimulation exhibit improved visual function as a result of the physical stimulation.

[0010] Both of these aspects of the invention may have the following characteristics. Conditions that result in damaged retinas that may be treated with the various embodiments of uses of the sources of physical stimulation of the invention include age-related macular degeneration, retinitis pigmentosa, long-term retinal detachment, diabetic retinopathies, Stargardt's retinopathy, Leber's congenital amaurosis, Best's Disease, and choroidal disease or damage. Physical stimulation may be, for example, provided to the retina or eye. Suitable devices that provide chronic physical stimulation may be constructed of a material that is electrically

inert. The implant may also be fenestrated. Suitable locations of the eye for stimulation include, but are not limited to, the subretinal space, the epiretinal space, the subscleral space, the subconjunctival space, the vitreous cavity and the anterior chamber.

[0011] In all aspects of the invention, the devices used for producing an implant for improving visual function of a damaged retina may be adapted to be surgically implanted into the subretinal space at an angle between about 5° and 80° off-axis from a macula, wherein the angle is defined by an intersection of an axis line extending from the macula to a central portion of a pupil, and an off-axis line extending from the device to the central portion of the pupil. The device (with or without at least one fenestration) may be adapted to be surgically implanted in at least one sector of a retina, excluding the macula. The device or devices may be adapted to be implanted in the temporal or nasal (or both) half retina region of the eye, or symmetrically around a region centered by the macula.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] **FIG. 1A** presents top cross-section of a human eye.

[0013] **FIG. 1B** presents a cross-section through the human eye that include the layers of the outer and inner anatomical retina, as indicated by the inset of **FIG. 1A**.

[0014] **FIG. 2** illustrates one preferred shape of an implantable device.

[0015] **FIG. 3** illustrates a first alternative shape of the implantable device of **FIG. 2**.

[0016] **FIG. 4** illustrates a second alternative shape of the implantable device of **FIG. 2**.

[0017] **FIG. 5** is a two dimensional array of implantable devices.

[0018] **FIG. 6** is a three dimensional array of implantable devices

[0019] **FIG. 7** is a cross-sectional view of an embodiment showing an array of retina stimulation devices positioned in an eye in the periphery and/or mid-periphery outside the macula.

DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

[0020] Many human retinal diseases cause vision loss by partial to complete destruction of the vascular layers of the eye that include the choroid and choriocapillaris, both of which nourish the outer anatomical retina and a portion of the inner anatomical retina of the eye. A number of other retinal diseases cause vision loss due to partial to complete degeneration of one or both of the two anatomical retinal layers directly, due to inherent abnormalities of these layers. The components of the retinal layers include Bruch's membrane and retinal pigment epithelium which comprise the "outer anatomical retinal layer", and the photoreceptor, outer nuclear, outer plexiform, inner nuclear, inner plexiform, amacrine cell, ganglion cell and nerve fiber layers which comprise the "inner anatomical retinal layer", also known as the "neuroretina". The outer portion of the neuroretina is comprised of the photoreceptor and bipolar cell layers and is also known as the "outer retina" which is to be distinguished from the "outer anatomical retinal layer" as defined above.

[0021] Loss of function of the outer retina is commonly the result of dysfunction of the outer anatomical retinal layer that provides nourishment to the outer retina and/or to direct defects of the outer retina itself. The final common result, however, is dysfunction of the outer retina that contains the light sensing cells, the photoreceptors. Some of these "outer retina" diseases include age-related macula degeneration, retinitis pigmentosa, choroidal disease, long-term retinal detachment, diabetic retinopathies, Stargardt's disease, choroideremia, Best's disease, and rupture of the choroid. The inner portion of the neuroretina, however, often remains functionally and anatomically quite intact and may be activated by the appropriate stimuli.

[0022] Although prosthetic electrical devices designed to replace damaged or missing retinal cells have been used to treat vision loss caused by outer retinal degeneration, physical stimulation to improve large areas of retinal cell visual function is novel. As a non-limiting explanation, the promotion of improved retinal cell visual function by physical stimulation may be explained by the stimulation of production and release of growth factors (GFs); more specifically, neurotrophic-type growth factors (NTGFs), by the stimulated retinas in response to the wounding or trauma inflicted by the physical stimulation. The synthesis and/or secretion of neurotrophic factors would then improve retinal cell function and survival in conditions where these activities would be lost.

[0023] Animal and human studies have be used to show that electrical stimulation may be used to improve the general inherent visual function of damaged retinal cells in direct contact with and surrounding an implanted electrical artificial silicon retina prosthesis (Chow et al., 2002). The mechanism of action may be related to the upregulation and production of endogenous survival-type factors by the retina due to an electrical effect on cellular membranes which may include a direct irritant effect of the electric current.

[0024] An irritant effect is also produced by the physical effect that includes a mechanical foreign-body effect, of an implant placed into or in contact with the retina. Such an irritant effect is akin to a mild damage effect on the retina which is known to upregulate the production of survival-type factors. For example, an incision into the retina, called a retinotomy, is known to upregulate, albeit temporarily, certain survival-type factors that also temporarily slow down retina degeneration in a rat model of retinal degeneration (Peng et al., 1997). A non-electrical foreign body that is inert or almost inert is therefore capable of producing a chronic irritant effect that chronically upregulates endogenous survival factors in the retina and to produce a long-term slow down or prevention of a retinal degenerative process.

[0025] A system and method are disclosed of placing a non-electrical physical and/or mechanical foreign body into or in contact with the retina to irritate and therefore chronically stimulate the upregulation of survival-type factors to slow down and/or prevent retinal degeneration. The subject matter of this application also includes the devices used to produce the said chronic irritation of the retina. Such non-electrical chronic irritant devices theoretically may have the ability to slow down the degeneration in other organ systems such as the central nervous system.

[0026] The present invention discloses both devices and novel methods to non-electrically irritate and/or stimulate the retina by physical and/or mechanical stimulation/irritation to improve large areas of retinal visual function and to protect the retina from degeneration.

[0027] Definitions

[0028] Subject/patient

[0029] A subject (patient) may be a human being or a non-human animal, but is preferably a human. Usually the individual has suffered some type of retinal damage and/or degeneration that results in some degree of visual loss and/or has a condition that will result in retinal damage and/or degeneration. A normal (healthy) subject does not have a condition that will result in retinal damage and/or degeneration and/or has not suffered retinal damage and/or degeneration.

[0030] Improving Visual Function

[0031] Improving visual function refers to improving a targeted function of the eye, selected by the artisan, and includes improving any to all of the following capabilities of the eye, retina and visual system: perception of brightness in the presence of light, perception of darkness in the absence of light, perceptions of contrast, color, shape, resolution, movement and visual field size.

[0032] Primary visual degradation means loss of visual function due to malfunctioning, damaged or degeneration of structures found in the eye. Secondary visual degradation means loss of visual function due to secondary damage, typically from lack of use of the vision-associated portions of the brain. Improving visual function means to improve the visual function of primary visual degradation, secondary visual degradation or both.

[0033] Eye/eyeball

[0034] The eye (or eyeball) has the usual definition in the art. Eye includes all interior and exterior surfaces, components, contents and cavities of the eye. The eye does not include the eyelid.

[0035] The retina of the eye can be divided into sectors as is commonly accepted in the art. Such sectors are described by the use of the terms temporal, nasal, superior, inferior, by clock hour designation, and by the number of degrees away from the macula. For example, the temporal sector of the retina is the retina temporal to a perpendicular plane cutting through retina from the 12 o'clock to the 6 o'clock positions and through the macula. In another example, the superior sector is the retina superior to a perpendicular plane cutting through the 9 o'clock to 3 o'clock positions and through the macula. In a further example, the superior-temporal sector is the intersection of these two sectors, a pie-shaped area delineated from the 9 o'clock position of the peripheral retina to the macula and then clockwise to the 12 o'clock position. More specific locations of the retina can be designated by degrees away from the macula and clock hour location: for example, 20 degrees away from the macula at the 3 o'clock (nasal) position. The number of degrees away from the macula is in visual axes degrees. These axes all intersect through the lens of the eye.

[0036] The visual field sectors correspond oppositely to the retinal sectors as is commonly understood in the art. For example, the superior-temporal sector of the retina corresponds to the inferior-nasal portion of the visual field.

[0037] Peripheral

[0038] To be peripheral to an object, device or other landmark includes all surrounding parts, but not the object, device or landmark, i.e., the object, device or landmark, together with the peripheral portion, constitutes the whole.

[0039] Light

[0040] Light refers not only to the electromagnetic spectrum that humans can readily perceive visually (approximately 400 nm to 750 nm), but also includes ultraviolet light (<400 nm in wavelength) as well as infrared light (>750 nm in wavelength).

[0041] Indications

[0042] The invention can be used to improve visual function in subjects in which the retina is damaged by disease, degeneration, condition, or trauma and/or to slow down or stop the progression of damage by disease, degeneration, condition or trauma. Common diseases, conditions, degeneration or trauma that are particularly amenable to this treatment include age-related macula degeneration, retinitis pigmentosa, Leber's congenital amaurosis, Stargardt's disease, Best's disease, diabetic retinopathy, long-term retinal detachment, and choroidal damage.

[0043] Eye Structure

[0044] Referring to the drawings, **FIG. 1A** illustrates a section through the eyeball. The neuroretina **150** comprises multiple layers of cells and structures (see **FIG. 1B**). The photoreceptor components of the retina are situated within the neuroretina which covers the internal posterior cavity of the eye, terminating anteriorly at the ora serrata **167**. The ciliary body **168** and the iris **162** are covered by extensions of the retina, lacking photoreceptor components. The outermost layers of the eye consist of the sclera **164** and cornea **158**. The sclera is pierced by the emerging optic nerve **166**. The lens **160** and vitreous cavity **154** are also indicated. The macula **169** of the retina is typically a 3 mm by 5 mm oval region, at the center of which is the fovea **170**.

[0045] The layers of the eye at the posterior pole from inside to outside are shown in **FIG. 1**B: internal limiting membrane **40**, nerve fiber layer **42**, ganglion and amacrine cell layer **44**, inner plexiform **46**, inner nuclear layer **48**, outer plexiform **50**, outer nuclear and bipolar cell layer **52**, and photoreceptor layer **54**, all of which constitute the anatomical inner retinal layer, also known as the neuroretina **56**. The retinal pigment epithelium **58**, and Bruch's membrane **60** constitute the outer retinal layer **62**. The choriocapillaris **64**, and choroid **66** comprise the choroidal vasculature **68**. The outer coat of the eye is the sclera **70**. Light **156** enters the retina as shown.

[0046] Devices and Methods to Provide Physical Stimulation

[0047] Any object that can provide a chronic or prolonged physical stimulation or irritation to the eye can be used as a source of physical stimulation. These devices may include, but are not limited to, electrically inert objects, mechanically or electrically activated objects, and chemical or biological agents. Several electrically activated devices, including retina stimulation devices (RSDs), have been used to pro-

vide electrical stimulation to an eye or the retina. For example, electrical devices previously described (Chow, U.S. Pat. No. 5,024,223, 1991; Chow and Chow, U.S. Pat. No. 5,397,350, 1995; Chow and Chow, U.S. Pat. No. 5,556, 423, 1996; Chow and Chow, 1997; Chow et al., 2001; Chow and Peachey, 1999; Chow and Chow, U.S. Pat. No. 5,895, 415, 1999; Chow and Chow, U.S. Pat. No. 6,230,057 B1, 2001), may be used. The entirety of the disclosure of each of these patents is incorporated herein by reference.

TABLE A

Device	References
Artificial Silicon Retina (ASR ™)	(Chow, U.S. Pat. No. 5,016,633, 1991; Chow, U.S. Pat. No. 5,024,223, 1991)
Independent Surface Electrode Microphotodiodes (ISEMCP)	(Chow and Chow, U.S. Pat. No. 5,397,350, 1995; Chow and Chow, U.S. Pat. No. 5,556,423, 1996)
Independent Surface Electrode Microphotodiodes with an electrical capacitor (ISEMCP-Cs)	(Chow and Chow, U.S. Pat. No. 5,397,350, 1995; Chow and Chow, U.S. Pat. No. 5,556,423, 1996)
Multi-phasic Photodiode Retinal Implants (MMRIs, such as MMRI-4)	(Chow and Chow, U.S. Pat. No. 5,895,415, 1999; Chow and Chow, U.S. Pat. No. 6,230,057 B1, 2001)
Variable Gain Multi-phasic Photodiode Retinal Implants (VGMMRIs)	(Chow and Chow, U.S. application No. 09/539,399, 2000)

[**0048**] As stated above, the physical stimulation may be provided by any object that can remain in physical contact with and/or irritate cells, such as retinal cells of an eye, for an extended period of time. The extended period of time may be years, such as would be the case with a device that would be implanted in the eye and persist indefinitely in the eye unless it was purposefully extracted. Alternatively, the extended period of time may be a limited time, for example one year, after which the implanted device or agent would biodegrade or otherwise be absorbed.

[**0049**] In one preferred embodiment, the source of physical stimulation is one or more devices or objects that is electrically inactive such that it is neither photoactive, a source of electrical stimulation, nor in electrical communication with a source of electrical stimulation. The device may be constructed from silicon, metal, plastic, ceramic, glass, wood, sand or any of a number of materials. For example, an object of any shape or depth may be used. These shapes may include, but not be limited to, to geometric shapes, such as straight lines, circles, squares, rectangles, and triangles as well as three-dimensional shapes, such as balls, cubes, cylinders, or cones.

[**0050**] Referring to FIGS. **2-4**, several suitable shapes of implantable devices are shown. The device may be a disk-shaped object **174** with or without fenestrations **176**, as shown in **FIG. 2**. In order to increase the surface area available to physically contact cells in the eye, the object **174** may be constructed to include various shape protrusions **178**. The object **180** shown in **FIG. 2** illustrates a spherical shape. Again, fenestrations **182** may be incorporated in the object to allow nutrients to pass through. Irregularly-shaped objects **184**, such as illustrated in **FIG. 4**, may be also be used. While the devices may be of various different dimensions, one preferred size range is greater than approximately 1 micron and less than approximately 20 mm in linear dimensions, and more preferrably greater than approximately 0.5 mm and less than approximately 5 mm in linear dimensions. Substrates for such objects include, without limitation, bio-absorbable polymers, silicon and other metals, and biomaterials. These devices can be implanted in the same region or regions of an eye as discussed for the RSDs. Many materials, shapes, sizes and devices may be used as long as they interact with cells in the eye to physically stimulate these cells. Also, in yet other embodiments, one or more electrically inert devices may be implanted in the eye in combination with one or more devices intended to supply electrical stimulation to the eye.

[**0051**] In yet other embodiments, the device may be an interconnected array of implantable elements. For example, **FIG. 5** shows a two dimensional array **190** of implantable objects **186** interconnected by a flexible biocompatible mesh **188**. Each of the objects **186** may be of the same or different shape and maintains its physical connection with one or more of the other objects while in the eye via the mesh **188**. Alternatively, as shown in **FIG. 6**, the array may be a three dimensional array **192** of implantable objects **186** interconnected by a flexible mesh **188**.

[**0052**] Other means to provide physical stimulation includes implanting devices that deliver an irritant. For example, oils, detergents, bile salts, etc. may be applied in small quantities that are yet sufficient to physically stimulate the cells. Preferably, the irritant is packaged, such as in a capsule, so that the irritant is slowly released over time, and so that the "packaging" is ultimately absorbed by the body. Examples of biodegradable substances include biodegradable polymers. Biodegradable polymers decompose when placed inside an organism and thus eliminate the need to remove the implant after the bioactive agent has been released, since the polymer will gradually break down and may be metabolized or excreted from the body. The decomposition of a biodegradable polymer can be observed as a decline in the molecular weight of the polymer over time. Polymer molecular weights can be determined by a variety of methods including size exclusion chromatography (SEC), and are generally expressed as weight averages or number averages. A polymer is biodegradable if, when in phosphate buffered saline (PBS) of pH 7.4 and a temperature of 37° C., its weight-average molecular weight is reduced by at least 25% over a period of 6 months as measured by SEC.

[**0053**] Polymers which could be useful as "packaging" capsules include, but are not limited to, polyesters, such as poly(caprolactone), poly(glycolic acid), poly(lactic acid), poly(hydroxybutryate); copolymers of caprolactone, glycolic acid, lactic acid, and hydroxybutryate; polyanhydrides, such as poly(adipic anhydride); poly(para-dioxanone); poly-(malic acid); polyamines; polyurethanes; polyesteramides; polyorthoesters; polyacetals; polyketals; polycarbonates; polyorthocarbonates; polyphosphazenes; poly(amino acids); chitin; chitosan; and copolymers and mixtures thereof.

[**0054**] Chemical or biological agents, including growth factors, can also be introduced into the eye to provide a prolonged stimulation to enhance rescue and retina functional improvement. This additional step is attractive because some factors, especially neurotrophictype growth factors, may improve retinal function and provide limited neuronal rescue in eyes with retinal degeneration and dysfunction. These growth factors include, but are not limited to, glial cell line-derived neurotrophic factor (GDNF), nerve

growth factor (NGF), brain derived neurotrophic growth factor (BDNGF), neurotropin-3 (NT-3), neurotropin-4 (NT-4), neurotropin-5 (NT-5), ciliary neurotropic factor (CNTF) and fibroblastic growth factor (FGF). These growth factors can be delivered to the eye by coating the RSD with growth factor(s) before implantation, by injection of the growth factor(s) into the locations of the subretinal space, vitreous cavity, subconjunctival space, subscleral space, and/or the anterior chamber either singly or in combination with each other, as a single dose or as multiple repeat doses before, during and/or after implantation of the RSD(s) or other electrical stimulating device.

[**0055**] Location of Stimuli

[**0056**] The chronic physical stimulation provided by at least one device may be provided subretinally, epiretinally, subsclerally (between the sclera and choroid), on the scleral surface, on the conjuctival surface and/or from or within any structure of the eye. Other means of providing physical simulation to the retina and eye may include devices that deliver chronic stimulation from the underside of the eyelid(s). Preferably, physical stimulation is from the subretinal space which is an area that is in a close proximity to the damaged retinal cells.

[**0057**] Therefore, in one embodiment, the chronically irritating/stimulating agent can be inserted in a way that it is placed in direct contact with the damaged retinal cells. In another embodiment, the chronically irritating/stimulating agent can be placed adjacent to, but not in direct contact with, the damaged retinal cells. In response to the prolonged trauma inflicted by the irritant, healthy retinal cells may be chronically stimulated to produce and release growth factors, such as neurotrophic growth factors, to help enhance retinal cell function.

[**0058**] Implantation Sites and Surgical Methods

[**0059**] In one embodiment, the physical stimulation is preferably in the subretinal space in the periphery and/or mid-periphery of the eye, outside of the macula. For devices that are implanted, more than one device may be implanted, if needed, in an eye to stimulate a larger area of the retina, and multiple devices can be implanted in paracentral locations such as one in each of the four paracentral quadrants, approximately, but not limited to, 5 to 80 degrees peripheral to the macula. In other embodiments, one or more devices may be implanted in the macular region of the eye. In one embodiment the implants may be placed in the subretinal space in the mid-periphery approximately 20 degrees away from the macula, using one device or up to approximately four devices evenly spaced on a perimeter in the midperiphery. Cells to stimulate include the remaining cells of the inner retina.

[**0060**] **FIG. 7** is a cross-sectional view of an eye **6** showing an array **200** of RSDs **10** in the subretinal space. Although RSDs **10** are discussed below with respect to **FIG. 7**, the implantation locations and techniques discussed apply equally to the other types of implantable objects and agents mentioned above. One or more RSDs may be spaced symmetrically around the macula in the peripheral or mid-peripheral regions of the eye in one embodiment. Alternatively, the RSDs may be spaced asymmetrically around the macula. In one embodiment, the RSDs are implanted at a position in the subretinal space between about a 5 degrees and an 80 degrees angle off-axis from the macula, where the angle is defined by an intersection of an axis line extending from the macula to a central portion of the pupil and an off-axis line extending from the retina stimulation device to the central portion of the pupil. The RSDs may also be implanted in the temporal half retina region and/or nasal half retina region, within the subretinal space. Any of a number of techniques and instruments may be used to perform the implantation into the subretinal space (Chow, U.S. Pat. No. 5,024,223, 1991; Chow and Chow, U.S. Pat. No. 5,397,350, 1995).

[**0061**] In yet another embodiment, an implantable device is designed to be implanted onto the epiretinal surface (i.e. on the nerve fiber layer side) of the retina. It is retained in position by retinal tacks, biocompatible glues, or other means. In the case of electrical implantable devices, subconjunctival/scleral placement of the device results in less efficient electrical stimulation of the retina compared to a subretinally or epiretinally placed device, but the extraocular location of the device decreases the surgical risk to a patient since intraocular surgery would not be required for its implantation. The subconjunctival/scleral placement of a device also allows a stable device position to be achieved without fixating devices or glues (i.e., the device is held in place between the conjunctiva and sclera).

[**0062**] Surgical methods are well known in the art (Peyman et al., 2000). Descriptions of specific surgeries for RSD implantation, which are also applicable to other physical stimulating devices, have been extensively described (Chow, U.S. Pat. No. 5,024,223, 1991; Chow and Chow, U.S. Pat. No. 5,397,350, 1995; Chow and Chow, U.S. Pat. No. 5,556,423, 1996; Chow and Chow, 1997; Chow et al., 2001; Chow and Peachey, 1999; Chow and Chow, U.S. Pat. No. 5,895,415,1999; Chow and Chow, U.S. Pat. No. 6,230, 057 B1, 2001).

[**0063**] For example, direct insertion may be accomplished as follows: the device or plurality of devices is inserted into the vitreous cavity of the eye through a pars plana incision. A horizontal incision is then made through the retina from the vitreous side in the temporal portion of the posterior pole into the potential space between the photoreceptor layer and the retinal pigment epithelium. A horizontal incision made at this location avoids cutting inner retinal vasculature and is parallel to coursing nerve fiber layers, therefore also avoiding their injury. Illumination for surgery is provided by an optical fiber light pipe. The potential space is then be opened by cannula irrigation of a balanced salt solution into the subretinal space.

[**0064**] The device is then placed into the subretinal cavity at the posterior pole under the macula area. Specifically, the device is placed between the retinal pigment epithelium and photoreceptor layer, or if the photoreceptor layer is atrophied or lost, then between the retinal pigment epithelium and the bipolar and horizontal cell layer. The device is positioned such that the electrical ground(s) is overlaying the retinal pigment epithelium, and the active electrode(s) faces incident light.

[**0065**] After insertion, a series of endolaserphotocoagulation or endocautery burns may be made around the periphery of the device to secure the device, although these burns may not be necessary in many cases. The scar tissue so formed around the periphery of the device by these burns may

prevent the device from moving out of position in some patients. Endolaserphotocoagulation or endoelectrocautery may also be used to seal the retinal incision. Air or other medically approved gaseous compounds may also be injected into the vitreous cavity to tamponade the retinal opening during healing. The pars plana incision is then closed in the usual surgical manner.

[0066] An alternate method for implantation of a device involves making an incision through the sclera just posterior to the ora serata. Dissection proceeds through the choroid, choriocapillaris, Bruch's membrane and retinal pigment epithelium under stereo operating microscope control into the potential space between the inner and outer anatomical retinal layers. The artificial retinal implant is then inserted into this space and directed posteriorly towards the macula by a pushing action imparted by a formed curved iris spatula or by use of an insertion guide. The RSD or other implantable device rests in the retinal periphery of the eye between the inner and outer anatomical retinal layers.

[0067] In another approach, some devices can be implanted by simple injection into the subretinal space through cannulas. Preferably, the devices are placed in a vehicle such as a biocompatible liquid and injected into the subretinal space via a retinotomy incision using a cannula. Such a liquid vehicle may be a balanced salt solution or a more viscous material like methylcellulose.

[0068] The retina is preferably illuminated by a light pipe to facilitate the injection of the devices. The cannula is introduced into the vitreous cavity of the eye via a pars plana incision. Dissection of the posterior vitreous is performed to separate the posterior hyaloid face from the retinal surface along with a vitrectomy. A small retinotomy incision is made through the retina following the direction of the nerve fiber layer using a stiletto type MVR blade. Dissection of the inner retina from the outer retinal layers is accomplished hydrostatically with the cannula using a fluid such as saline.

[0069] When the retinal areas to be implanted have been prepared with cannula hydro-dissection, the liquid vehicle with suspended devices is injected. An attempt should be made to distribute the suspended devices in a uniform monolayer. The cannula is then withdrawn, and a heavier-than-water non-miscible material (preferably, a perfluorocarbon) is placed over the posterior pole of the vitreous cavity to aid settling the retina. The non-miscible material is preferably removed after an appropriate time, usually 15 to 20 minutes, leaving a reattached retina. Alternatively, air may also be used to settle the retina. With settling and reattachment of the retina, the implanted devices tend to distribute into the desired monolayer.

[0070] Other surgical procedures and related materials will be evident to one of skill in the art and depend in part on the design of the device and the subject to be implanted.

[0071] In another embodiment, electrically inert objects, chemical, and/or biological agents can be inserted into an eye in several ways. Chemical and biological agents, such as growth factors, can be delivered to the eye by coating a substrate with these factor(s) before implantation and/or by injecting these factor(s) into the locations of the subretinal space, vitreous cavity, subconjunctival space, subscleral space, and/or the anterior chamber either singly or in combination with each other, as a single dose or as multiple repeat doses independent of, before, during and/or after implantation of the coated substrate or other electrical stimulating device. Electrically inert object(s) can be delivered to the eye by placing it directly into the subretinal space, vitreous cavity, subconjunctival space, subscleral space, and/or the anterior chamber through implantation or injection performed as previously described for the retinal implantable devices.

[0072] Demonstration of Efficacy

[0073] The demonstration of safety and efficacy of a preferred embodiment of this invention has been shown in multiple persons with retinal dysfunction that have been implanted with RSDs in the subretinal space as part of a clinical study to evaluate the feasibility of and effectiveness of these devices to act as prostheses. All persons so implanted have reported no complications and have reported improved levels of visual function subsequent to the placement of the RSDs. Such improvements have included improved perception of light, darkness, contrast, shape, resolution, color, motion, and visual field size. It will be appreciated by those of skill in the art that the improved levels of visual function reported represent results of RSDs and methods discovered by the inventors to function well in the practice of the invention. However, those skilled in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention. For example, a variety of mechanically and/or physically inert to partially inert materials can be used. Moreover, a variety of sizes and shapes of the RSD can be used. The RSD can also be inserted into various structures of the eye.

EQUIVALENTS

[0074] Although particular embodiments have been disclosed herein in detail, this has been done for purposes of illustration only and is not intended to be limiting with respect to the scope of the appended claims that follow. In particular, it is contemplated by the inventors that various substitutions, alterations, and modifications may be made to the invention without departing from the spirit and scope of the invention as defined by the claims. Other aspects, advantages, and modifications are considered to be within the scope of the following claims.

REFERENCES

[0075] Acheson, A., P. A. Barker, R. F. Alderson, F. D. Miller, et al. 1991. Detection of brain-derived neurotrophic factor-like activity in fibroblasts and Schwann cells: inhibition by antibodies to NGF. *Neuron.* 7:265-75.

[0076] Bosco, A., and R. Linden. 1999. BDNF and NT-4 differentially modulate neurite outgrowth in developing retinal ganglion cells. *J Neurosci Res.* 57:759-69.

[0077] Caleo, M., C. Lodovichi, and L. Maffei. 1999. Effects of nerve growth factor on visual cortical plasticity require afferent electrical activity. *Eur J Neurosci.* 11:2979-84.

[0078] Carmignoto, G., L. Maffei, P. Candeo, R. Canella, et al. 1989. Effect of NGF on the survival of rat retinal ganglion cells following optic nerve section. *J Neurosci.* 9:1263-72.

[0079] Chow, A. U.S. Pat. No. 5,016,633. 1991. Artifical retina device.

[0080] Chow, A. U.S. Pat. No. 5,024,223. 1991. Artificial retina device.

[0081] Chow, A., and V. Chow. U.S. Pat. No. 5,397,350. 1995. Independent photoelectric artificial retina device and method of using same.

[0082] Chow, A., and V. Chow. U.S. Pat. No. 5,556,423. 1996. Independent photoelectric artificial retina device and method of using same.

[0083] Chow, A., and V. Chow. U.S. Pat. No. 5,837,995. 1998. Wavelength-controllable Voltage-phase Photodiode Optoelectronic Switch ("Opsistor").

[0084] Chow, A., and V. Chow. U.S. application Ser. No. 09/564,841. A1. Artificial retina device with stimulating and ground return electrodes disposed on opposite sides of the neuroretina and method of attachment.

[0085] Chow, A. Y., and V. Y. Chow. 1997. Subretinal electrical stimulation of the rabbit retina. *Neurosci Lett.* 225:13-6.

[0086] Chow, A. Y., M. T. Pardue, V. Y. Chow, G. A. Peyman, et al. 2001. Implantation of silicon chip microphotodiode arrays into the cat subretinal space. *IEEE Trans Neural Syst Rehabil Eng.* 9:86-95.

[0087] Chow, A. Y., and N. Peachey. 1999. The subretinal microphotodiode array retinal prosthesis II. *Ophthalmic Res.* 31:246.

[0088] Chow, V., and A. Chow. U.S. Pat. No. 5,895,415. 1999. Multi-phasic microphotodiode retinal implant and adaptive imaging retinal stimulation system.

[0089] Chow, A. Y., V. Y. Chow, G. A. Peyman, et al. 2002. Safety, Feasibility and Efficacy of Subretinal Artificial Silicon Retina Prosthesis for the Treatment of Patients with Retinitis Pigmentosa. Assoc Res Vision Ophth Meeting 2002. Abstract #835.

[0090] Chow, V., and A. Chow. U.S. application Ser. No. 09/539,399 (Allowed). 2000. Multi-Phasic Microphotodetector Retinal Implant with Variable Voltage and Current Capability and Apparatus for Insertion.

[0091] Chow, V., and A. Chow. U.S. Pat. No. 6,230,057 B1. 2001. Multi-phasic microphotodiode retinal implant and adaptive imaging retinal stimulation system.

[0092] Cui, Q., K. F. So, and H. K. Yip. 1998. Major biological effects of neurotrophic factors on retinal ganglion cells in mammals. *Biol Signals Recept.* 7:220-6.

[0093] Dooley, D. M., J. Sharkey, W. Keller, and M. Kasprak. 1978. Treatment of demyelinating and degenerative diseases by electro stimulation of the spinal cord. *Med Prog Technol.* 6:1-14.

[0094] Evans, R. D., D. Foltz, and K. Foltz. 2001. Electrical stimulation with bone and wound healing. *Clin Podiatr Med Surg.* 18:79-95, vi.

[0095] Frasson, M., S. Picaud, T. Leveillard, M. Simonutti, et al. 1999. Glial cell line-derived neurotrophic factor induces histologic and functional protection of rod photoreceptors in the rd/rd mouse. *Invest Ophthalmol Vis Sci.* 40:2724-34.

[0096] Kane, W. J. 1988. Direct current electrical bone growth stimulation for spinal fusion. *Spine.* 13:363-5.

[0097] Koyama, S., T. Haruyama, E. Kobatake, and M. Aizawa. 1997. Electrically induced NGF production by astroglial cells. *Nat Biotechnol.* 15:164-6.

[0098] Lagey, C. L., J. M. Roelofs, L. W. Janssen, M. Breedijk, et al. 1986. Electrical stimulation of bone growth with direct current. *Clin Orthop:*303-12.

[0099] Lambiase, A., and L. Aloe. 1996. Nerve growth factor delays retinal degeneration in C3H mice. *Graefes Arch Clin Exp Ophthalmol.* 234 Suppl 1:S96-100.

[0100] Leake, P. A., G. T. Hradek, S. J. Rebscher, and R. L. Snyder. 1991. Chronic intracochlear electrical stimulation induces selective survival of spiral ganglion neurons in neonatally deafened cats. *Hear Res.* 54:251-71.

[0101] Leake, P. A., G. T. Hradek, and R. L. Snyder. 1999. Chronic electrical stimulation by a cochlear implant promotes survival of spiral ganglion neurons after neonatal deafness. *J Comp Neurol.* 412:543-62.

[0102] Neely, M. D., and J. G. Nicholls. 1995. Electrical activity, growth cone motility and the cytoskeleton. *J Exp Biol.* 198:1433-46.

[0103] Peachey, N. S., and A. Y. Chow. 1999. Subretinal implantation of semiconductor-based photodiodes: progress and challenges. J Rehabil Res Dev. 36:371-6.

[0104] Peng, M., C. Liu, and R. Wen. 1997. Increase in bFGF and CNTF proteins in rat retina induced by mechanical injury. Invest Ophthalmol Vis. Sci. 38:S604.

[0105] Peyman, G., S. Meffert, M. Conway, and F. Chou. 2000. Advanced vitreoretinal surgical techniques. Martin Dunitz, Ltd, London. 624 pp.

[0106] Politis, M. J., and M. F. Zanakis. 1988a. Short term efficacy of applied electric fields in the repair of the damaged rodent spinal cord: behavioral and morphological results. *Neurosurgery.* 23:582-8.

[0107] Politis, M. J., and M. F. Zanakis. 1988b. Treatment of the damaged rat hippocampus with a locally applied electric field. *Exp Brain Res.* 71:223-6.

[0108] Politis, M. J., and M. F. Zanakis. 1989. The short-term effects of delayed application of electric fields in the damaged rodent spinal cord. *Neurosurgery.* 25:71-5.

[0109] Politis, M. J., M. F. Zanakis, and B. J. Albala. 1988a. Facilitated regeneration in the rat peripheral nervous system using applied electric fields. *J Trauma.* 28:1375-81.

[0110] Politis, M. J., M. F. Zanakis, and B. J. Albala. 1988b. Mammalian optic nerve regeneration following the application of electric fields. *J Trauma.* 28:1548-52.

[0111] Reh, T. A., K. McCabe, M. W. Kelley, and O. Bermingham-McDonogh. 1996. Growth factors in the treatment of degenerative retinal disorders. *Ciba Found Symp.* 196:120-31.

1. A method of improving visual function of a damaged and/or degenerating retina in a human eye, the method comprising:

applying at least one of a chronic physical and mechanical stimulation to the eye to improve or maintain visual function of the retina, wherein applying the at least one of the chronic physical and mechanical stimulation improves visual function of at least one structure of the damaged retina.

2. The method of claim 1, wherein the improved visual function comprises at least one of improved perception of light in the presence of light, improved perception of darkness in the presence of darkness, improved perception of contrast, color, shape, resolution, movement and visual field size.

3. The method of claim 1, wherein the chronic physical stimulation is applied by a source of physical stimulation comprising at least one device in contact with any structure of the eye.

4. The method of claim 1, wherein the chronic physical stimulation is provided to at least one of the damaged retina and a structure of the eye.

5. The method of claim 3, wherein the at least one device comprises a plurality of devices.

6. The method of claim 3, wherein the at least one device comprises one of an electrically inert device, a chemical agent and a biological agent.

7. The method of claim 1, wherein the source of physical stimulation comprises a device having at least one photoactive surface electrically connected to at least one stimulating electrode.

8. The method of claim 7, wherein the photoactive surface comprises at least one photodiode, photovoltaic device or photoelectric device.

9. The method of claim 8, wherein the at least one photodiode comprises a plurality of photodiodes, photovoltaic devices or photoelectric devices.

10. The method of claim 3, wherein the at least one device is implanted surgically into a subretinal space at an angle between about 5° and 80° off-axis from a macula, wherein the angle is defined by an intersection of an axis line extending from the macula to a central structure of a pupil and an off-axis line extending from the device to the central structure of the pupil.

11. The method of claim 3, wherein the at least one device is surgically implanted in at least one area of the damaged retina, excluding a macula.

12. The method of claim 3, wherein the at least one device comprises at least one fenestration.

13. The method of claim 1, wherein the damaged retina is the result of at least one condition selected from the group consisting of age-related macular degeneration, retinitis pigmentosa, choroidal disease, choroidaremia, long-term retinal detachment, diabetic retinopathies, Stargardt's retinopathy, Leber's congenital amaurosis, Best's Disease, choroidal rupture, and choroidal disease.

14. A method of treating visual degradation resulting from a damaged retina, wherein the visual degradation comprises primary or secondary degradation, the method comprising:

applying chronic physical stimulation to an eye containing the damaged retina.

15. The method of claim 14, wherein the damaged retina comprises a damaged cell comprising at least one of a photoreceptor cell, choroidal vasculature cell, retinal pigment epithelial cell, bipolar cell, horizontal cell, amacrine cells and ganglion cells; and

wherein at least one portion of the damaged cell is treated.

16. The method of claim 15, wherein the at least one portion that is treated comprises at least one portion of an undamaged cell.

17. The method of claim 15, wherein the at least one portion that is treated comprises a portion not in physical contact with a source of chronic physical stimulation.

18. The method of any of claims **14-17**, wherein the physical stimulation is provided to at least one of the damaged retina and a structure of the eye.

19. The method of claim 14, wherein applying chronic physical stimulation comprises placing a source of physical stimulation in contact with the eye, the source of physical stimulation comprising at least one device.

20. The method of claim 19, wherein the at least one device is in contact with the retina, and the applying physical stimulation treats at least one of a structure of the damaged retina peripheral to the portion of the retina in contact with the at least one device and a portion of the damaged retina in contact with the device.

21. The method of claim 19, wherein the at least one device comprises a plurality of devices.

22. The method of claim 19, wherein the at least one device comprises one of an electrically inert object, a chemical agent and a biological agent.

23. The method of claim 19, wherein the at least one device comprises at least one photoactive surface electrically connected to at least one stimulating electrode.

24. The method of claim 23, wherein the at least one photoactive surface comprises at least one photodiode, photovoltaic device or photoelectric device.

25. The method of claim 24, wherein the at least one photoactive surface comprises a plurality of photodiodes, photovoltaic devices, or photoelectric devices.

26. The method of claim 19, wherein the at least one device is implanted surgically into a subretinal space at an angle between about 5° and 80° off-axis from a macula, wherein the angle is defined by an intersection of an axis line extending from the macula to a central structure of a pupil, and an off-axis line extending from the device to the central structure of the pupil.

27. The method of claim 19, wherein the at least one device is surgically implanted in at least one area of the retina, excluding a macula.

28. The method of claim 14, wherein the physical stimulation is intermittent.

29. The method of claim 14, wherein said damaged retina is the result of at least one condition selected from the group consisting of age-related macular degeneration, retinitis pigmentosa, choroidal disease, choroidaremia, long-term retinal detachment, diabetic retinopathies, Stargardt's retinopathy, Leber's congenital amaurosis, Best's Disease and choroidal rupture.

30. A method of improving visual function in a damaged macula of a human eye, the method comprising:

selecting at least one electrically inert device;

implanting the at least one electrically inert device in a subretinal space in the eye; and wherein the device is positioned peripheral to the macula of the eye and in the subretinal space.

31. The method of claim 30, wherein implanting the at least one electrically inert device comprises implanting the device at a position in the subretinal space at an angle between about 5° and 80° off-axis from the macula, wherein the angle is defined by an intersection of an axis line extending from the macula to a central structure of the pupil and an off-axis line extending from the device to the central structure of the pupil.

32. The method of claim 30, wherein implanting the device further comprises implanting the device in a temporal half retina region of the eye.

33. The method of claim 30, wherein implanting the device further comprises implanting the device in a nasal half retina region of the eye.

34. The method of claim 30, wherein selecting at least one electrically inert device comprises selecting a plurality of electrically inert devices, and wherein implanting the at least one device comprises implanting the plurality of electrically inert devices.

35. The method of claim 34, wherein implanting each of the plurality of electrically inert devices comprises implanting each of the plurality of electrically inert devices at a respective position in the subretinal space at an angle between about 50 and 800 off-axis from the macula, wherein the angle is defined by an intersection of an axis line extending from the macula to a central structure of the pupil and an off-axis line extending from the device to the central structure of the pupil.

36. The method of claim 34, wherein implanting the plurality of electrically inert devices further comprises implanting the plurality of electrically inert devices in a temporal region of the eye.

37. The method of claim 34, wherein implanting the plurality of electrically inert devices further comprises implanting the plurality of electrically inert devices in a nasal region of the eye.

38. The method of claim 34, wherein the plurality of electrically inert devices are implanted symmetrically around a region centered by the macula.

39. A method of implanting an physically stimulating device in an eye of a patient having least one condition selected from the group consisting of outer neuroretina disease, choroidal disease and retinal epithelial disease, the method comprising:

implanting in a subretinal space in the eye of the patient at least one electrically inert device configured to contact a plurality of cells in the eye.

40. The method of claim 39, wherein the device is positioned in one of a peripheral or mid-peripheral region in the subretinal space outside of a macula of the eye.

41. The method of claim 39, wherein implanting the device comprises implanting the device at a position in the subretinal space at an angle between about 50 and 800 off-axis from the macula, wherein the angle is defined by an intersection of an axis line extending from the macula to a central structure of the pupil and an off-axis line extending from the device to the central structure of the pupil.

42. The method of claim 39, wherein implanting the device further comprises implanting the device in a temporal half retina region of the eye.

43. The method of claim 39, wherein implanting the device further comprises implanting the device in a nasal half retina region of the eye.

44. The method of claim 39, wherein the condition is selected from the group consisting of age-related macular degeneration, retinitis pigmentosa, choroidal disease, choroidaremia, long-term retinal detachment, diabetic retinopathies, Stargardt's retinopathy, Leber's congenital amaurosis, Best's Disease and choroidal rupture.

45. The method of claim 39, wherein implanting the at least one electrically inert device comprises implanting the plurality of devices.

46. Use of a source of physical stimulation for producing an implant for improving the visual function of a damaged retina in a human eye by applying chronic physical stimulation to the eye,

47. The use of claim 46, wherein applying chronic physical stimulation improves visual function of at least one structure which is not in contact with the source of physical stimulation.

48. The use of claim 46, wherein the improved visual function comprises at least one of improved perception of light in the presence of light, and improved perception of darkness in the presence of darkness, improved perception of contrast, color, shape, resolution, movement and visual field size.

49. The use of claim 46, wherein the source of physical stimulation comprises at least one device in contact with any structure of the eye.

50. The use of claim 46, wherein the physical stimulation is provided to at least one of the damaged retina and a structure of the eye.

51. The use of claim 46, wherein the at least one device is adapted to be in contact with the damaged retina, and the applying chronic physical stimulation improves the visual function of at least a structure of the damaged retina peripheral to a portion of the retina in contact with the at least one device.

52. The use of claim 49, wherein the at least one device comprises a plurality of devices.

53. The use of claim 49, wherein the at least one device comprises an electrically inert device.

* * * * *