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(54) **Titre : THERAPIES OPTOGENETIQUES POUR TROUBLES DU MOUVEMENT**
(54) **Title: OPTOGENETIC THERAPIES FOR MOVEMENT DISORDERS**

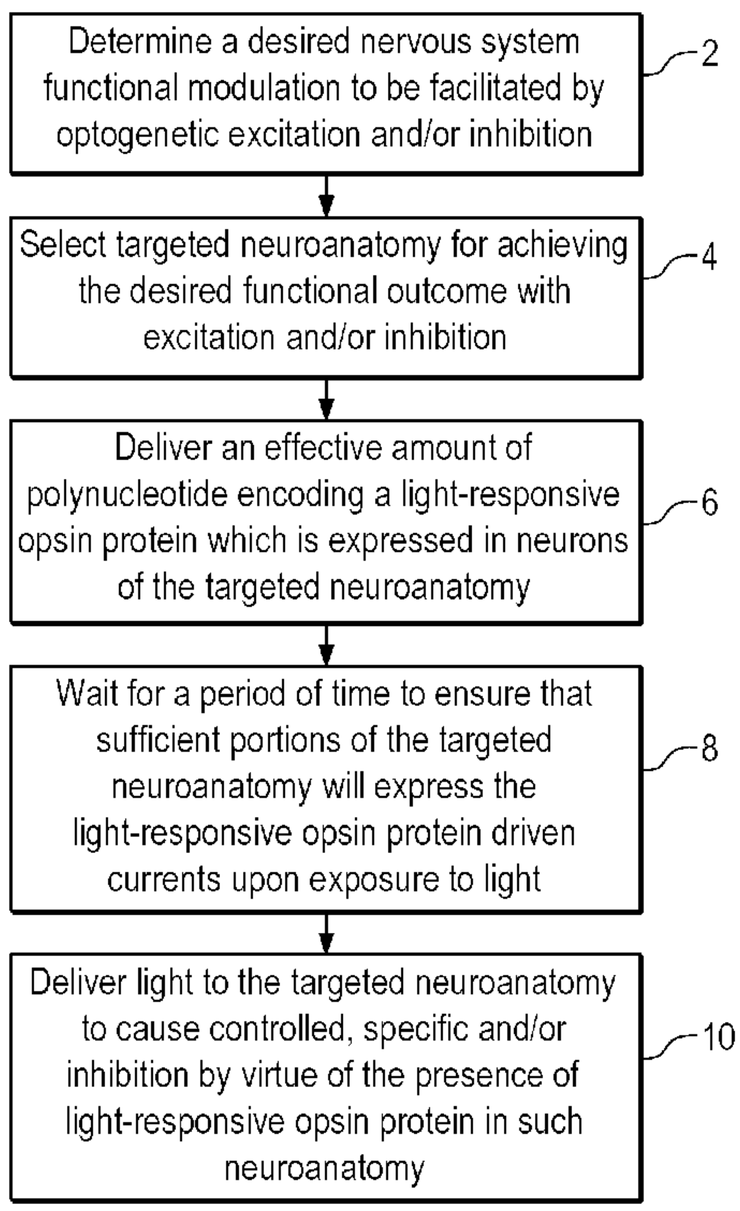

FIG. 1

(57) **Abrégé/Abstract:**
One embodiment is directed to a system for controllably managing motor function in the central nervous system of a patient having a targeted tissue structure that has been genetically modified to have light sensitive protein, comprising a light delivery element

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(57) **Abrégé(suite)/Abstract(continued):**
configured to direct radiation to at least a portion of a targeted tissue structure; a light source configured to provide light to the light delivery element; and a controller operatively coupled to light source; wherein the targeted tissue structure is a portion of the basal ganglia of the patient; and wherein the controller is configured to be automatically operated to illuminate the targeted tissue structure with radiation such that a membrane potential of cells comprising the targeted tissue structure is modulated at least in part due to exposure of the light sensitive protein to the radiation.

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[Continued on next page]

(54) **Title**: OPTOGENETIC THERAPIES FOR MOVEMENT DISORDERS

(57) **Abstract**: One embodiment is directed to a system for controllably managing motor function in the central nervous system of a patient having a targeted tissue structure that has been genetically modified to have light sensitive protein, comprising a light delivery element configured to direct radiation to at least a portion of a targeted tissue structure; a light source configured to provide light to the light delivery element; and a controller operatively coupled to light source; wherein the targeted tissue structure is a portion of the basal ganglia of the patient; and wherein the controller is configured to be automatically operated to illuminate the targeted tissue structure with radiation such that a membrane potential of cells comprising the targeted tissue structure is modulated at least in part due to exposure of the light sensitive protein to the radiation.

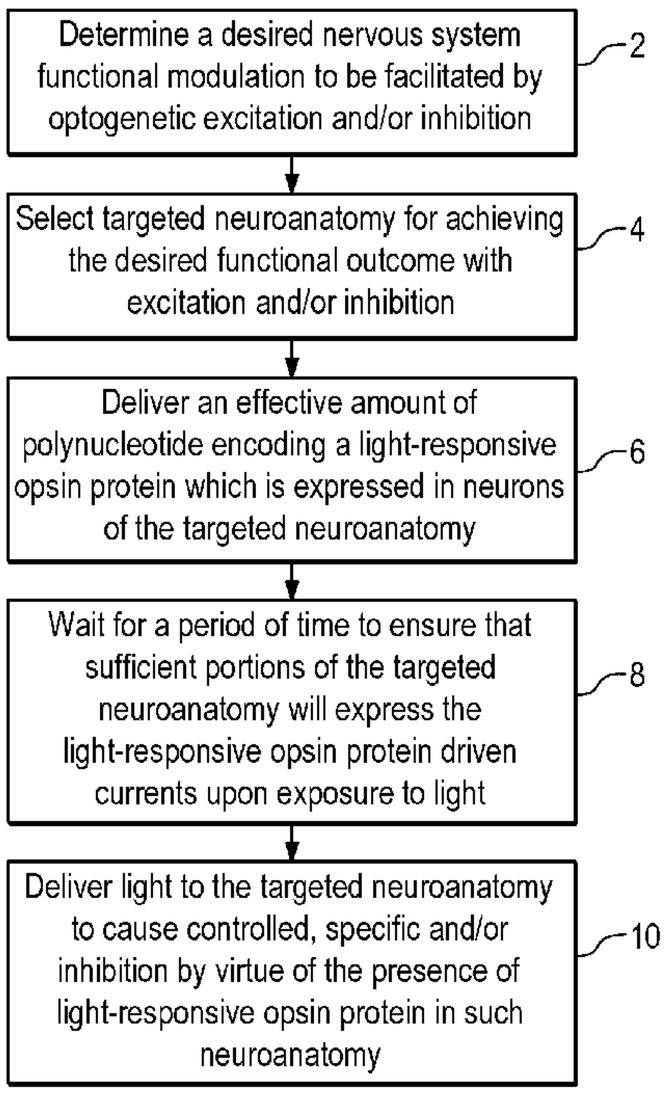

FIG. 1

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CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 137

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OPTOGENETIC THERAPIES FOR MOVEMENT DISORDERS

RELATED APPLICATION DATA

The present application claims priority to U.S. Provisional Application Serial No. 62/010,967, filed June 11, 2014. The foregoing application is hereby incorporated by reference into the present application in its entirety.

INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

Incorporated by reference in its entirety is a computer-readable nucleotide/ amino acid sequence listing submitted concurrently herewith, and identified as follows: One 156 KiloByte ASCII (Text) file named "20041_SeqList_ST25.txt" created on June 11, 2015

FIELD OF THE INVENTION

The present invention relates generally to systems, devices, and processes for facilitating various levels of control over cells and tissues in vivo, and more particularly to systems and methods for physiologic intervention wherein light may be utilized as an input to tissues which have been modified to become light sensitive.

BACKGROUND

Pharmacological and direct electrical neuromodulation techniques have been employed in various interventional settings to address challenges such as prolonged orthopaedic pain, epilepsy, and hypertension. Pharmacological manipulations of the neural system may be targeted to certain specific cell types, and may have relatively significant physiologic impacts, but they typically act on a time scale of minutes, whereas neurons physiologically act on a time scale of milliseconds. Electrical stimulation techniques, on the other hand, may be more precise from an interventional time scale perspective, but they generally are not cell type specific and may therefore involve significant clinical downsides.

Parkinson's disease is a movement disorder resulting from the loss of dopaminergic cells in the substantia nigra pars compacta (SNc). The consequence of SNc loss is a dysregulation of circuitry which regulates movement. Current medications are designed to replace or augment lost dopamine and are generally effective at improving symptoms early in the disease, but over time, many patients become resistant to medical therapy or develop complications of medical therapy. An alternative for these patients is deep brain stimulation (DBS), which generally does not completely reverse symptoms but in appropriate patients, this can improve symptoms and reduce some medical complications by focally modulating firing of neurons within the relevant circuits using an electrical stimulation implant. However, not all patients benefit equally from this therapy, likely due to incomplete restoration of normal functioning of the entire circuitry, and therapy can also be limited by adverse

effects due to non-specific electrical modulation of undesirable targets, such as adjacent axonal connections which serve other purposes (such as sensation, eye movements, anxiety and voice control). Therefore, there is a need for novel, improved therapies which will provide more biologically specific, focal restoration of circuit function in PD to improve therapeutic efficacy while reducing adverse effects.

A new neurointerventional field termed "Optogenetics" is being developed which involves the use of light-sensitive proteins, configurations for delivering related genes in a very specific way to targeted cells, and targeted illumination techniques to produce interventional tools with both low latency from a time scale perspective, and also high specificity from a cell type perspective.

For example, optogenetic technologies and techniques have been utilized in laboratory settings to change the membrane voltage potentials of excitable cells, such as neurons, and to study the behavior of such neurons before and after exposure to light of various wavelengths. In neurons, membrane depolarization leads to the activation of transient electrical signals (also called action potentials or "spikes"), which are the basis of neuronal communication. Conversely, membrane hyperpolarization leads to the inhibition of such signals. By exogenously expressing light-activated proteins that change the membrane potential in neurons, light can be utilized as a triggering means to induce inhibition or excitation. Thus optogenetic therapies generally involve delivery of a light-sensitive ion channel or pump to a cell, which will then promote

flux of specific ions across a cell membrane in response to specific wavelengths of light.

One example is channelrhodopsin (ChR) which is a light sensitive cation channel which, in response to blue light, opens and permits flow of sodium (Na+) ions across the cell membrane. In neurons, this causes depolarization and activation of the neuron containing this channel. An alternative example is halorhodopsin (NpHR, derived from the halobacterium *Natronomonas pharaonis*), a light-sensitive anion pump which pumps chloride (Cl-) ions into a cell in response to yellow light. When the cell is a neuron, NpHR will hyperpolarize the cell, thereby inhibiting it. In the context of optogenetic application, NpHR acts as an electrogenic chloride pump to increase the separation of charge across the plasma membrane of the targeted cell upon activation by yellow light. NpHR is a true pump and requires constant light to move through its photocycle. Since 2007, a number of modifications to NpHR have been made to improve its function. Codon-optimization of the DNA sequence followed by enhancement of its subcellular trafficking (eNpHR2.0 and eNpHR3.0) resulted in improved membrane targeting and higher currents more suitable for use in mammalian tissue. In addition, proton pumps archaerhodopsin-3 (“Arch”) and "eARCH", and ArchT, Leptosphaeria maculans fungal opsins (“Mac”), enhanced bacteriorhodopsin (“eBR”), and Guillardia theta rhodopsin-3 (“GtR3”) have been developed as optogenetic tools. As described in further detail below, these optogenetic proteins, when activated by light, may be used to hyperpolarize the targeted cells by pumping hydrogen ions out of such cells. A new class of channel, recently described by Karl Deisseroth et al, such as in Science. April 2014. 344(6182):420-4, and Jonas

Weitek, et al, in Science. April 2014. 344(6182):409-12, in which are incorporated by reference in their entirety, that is based on ChR but is modified to permit cations to pass through the "inhibitory" channel (which may be termed, by way of non-limiting examples; "iChR", "iC1C2", "ChloC", or "SwiChR") will open and permit large amounts of Cl- ions to pass, thereby hyperpolarizing the neuron more effectively and thus inhibiting the cell with greater efficiency and sensitivity. Thus this new class of channel, which is based on ChR (channel rhodopsin) but is modified to permit cations to pass through the channel rather than anions, provides yet further options. In response to blue light, this new "inhibitory" channel (iChR) will open and permit large amounts of Cl- ions to pass, thereby hyperpolarizing the neuron more effectively and thus inhibiting the cell with greater efficiency and sensitivity. When these opsins are transferred into neurons in the nervous system, those neurons can be activated or inactivated at will and with great efficiency and temporal control in response to specific wavelengths of light delivered by a light emitting device. Optogenetics therefore provides opportunities to regulate circuits with great biological specificity, so that only specific populations of neurons are activated or inhibited, without influencing nearby axons which are passing by and serve functions which are not intended targets of the therapy. This also provides opportunities for greater degree of restoration of broader circuit function by specific activating and/or inactivating multiple populations of neurons in a fashion that cannot be achieved with existing therapies.

SUMMARY

One embodiment is directed to a system for controllably managing motor function in the central nervous system of a patient having a targeted tissue structure that has been genetically modified to have light sensitive protein, comprising a light delivery element configured to direct radiation to at least a portion of a targeted tissue structure; a light source configured to provide light to the light delivery element; and a controller operatively coupled to light source; wherein the targeted tissue structure is a portion of the basal ganglia of the patient; and wherein the controller is configured to be automatically operated to illuminate the targeted tissue structure with radiation such that a membrane potential of cells comprising the targeted tissue structure is modulated at least in part due to exposure of the light sensitive protein to the radiation. The portion of the basal ganglia of the patient may be selected from the group consisting of: a subthalamic nucleus, a substantia nigra, a globus pallidus, a nucleus accumbens, and a putamen. An applicator may be disposed to illuminate the target tissue structure, the applicator being comprised of at least a light delivery element and a sensor, wherein the sensor is configured to: produce an electrical signal representative of the state of the target tissue or its environment; and deliver the signal to the controller, wherein the controller is further configured to interpret the signal from the sensor and adjust at least one light source output parameter such that the signal is maintained within a desired range, wherein the light source output parameter may be chosen from the group containing of; current, voltage, optical power, irradiance, pulse duration, pulse interval time, pulse

repetition frequency, and duty cycle. The sensor may be selected from the group consisting of: an optical sensor, a temperature sensor, a chemical sensor, and an electrical sensor. The controller further may be configured to drive the light source in a pulsatile fashion. The current pulses may be of a duration within the range of 1 millisecond to 100 seconds. The duty cycle of the current pulses may be within the range of 99% to 0.1%. The controller may be responsive to a patient input. The system may be configured such that patient input may trigger the delivery of current. The current controller further may be configured to control one or more variables selected from the group consisting of: the current amplitude, the pulse duration, the duty cycle, and the overall energy delivered. The light delivery element may be placed about at least 60% of circumference of a nerve or nerve bundle. The light sensitive protein may be an opsin protein. The opsin protein may be selected from the group consisting of: a depolarizing opsin, a hyperpolarizing opsin, a stimulatory opsin, an inhibitory opsin, a chimeric opsin, and a step-function opsin. The opsin protein may be selected from the group consisting of: NpHR, eNpHR 1.0, eNpHR 2.0, eNpHR 3.0, SwiChR, SwiChR 2.0, SwiChR 3.0, Mac, Mac 3.0, Arch, ArchT, Arch 3.0, ArchT 3.0, iChR, ChR2, C1V1-T, C1V1-TT, Chronos, Chrimson, ChrimsonR, CatCh, VChR1-SFO, ChR2-SFO, ChR2-SSFO, ChEF, ChIEF, Jaws, ChloC, Slow ChloC, iC1C2, iC1C2 2.0, and iC1C2 3.0. The light sensitive protein may be delivered to the target tissue using a virus. The virus may be selected from the group consisting of: AAV1, AAV2, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, lentivirus, and HSV. The virus may contain a polynucleotide that encodes for the opsin protein. The polynucleotide may encode for a transcription promoter. The transcription promoter may be selected from the group consisting

of: CaMKIIa, hSyn, CMV, Hb9Hb, Thy1, and Ef1a. The viral construct may be selected from the group consisting of: AAV1-hSyn-Arch3.0, AAV5-CamKII-Arch3.0, AAV1-hSyn-iC1C23.0, AAV5-CamKII- iC1C23.0, AAV1-hSyn-SwiChR3.0, and AAV5-CamKII-SwiChR3.0. The light source may be configured to emit light having a wavelength that is within a wavelength range that is selected from the group consisting of: 440nm to 490nm, 491nm to 540nm, 541nm to 600nm, 601nm to 650nm, and 651nm to 700nm. The light delivery element may comprise an optical fiber.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates one embodiment of a configuration for a light-based neuromodulation therapy.

Figure 2 depicts one embodiment of a system level componentry configuration for optogenetic treatment of a human in accordance with the present invention.

Figures 3A and 3B illustrate various aspects of opsin activation for certain opsin proteins which may be utilized in the present invention.

Figure 3C depicts an LED specification table for various LEDs that may be utilized in embodiments of the present invention.

Figure 4 depicts an embodiment of one portion of an illumination configuration for optogenetic treatment of a human in accordance with the present invention.

Figure 5 depicts a light power density chart that may be applied in embodiments of the present invention.

Figure 6 depicts an irradiance versus geometry chart that may be applied in embodiments of the present invention.

Figures 7-25 depict various aspects of embodiments of light delivery configurations which may be utilized for optogenetic treatment of a human in accordance with the present invention.

Figures 26A-37 depict various aspects of embodiments of light delivery system componentry and data, which may be utilized for optogenetic treatment of a human in accordance with the present invention.

Figures 38A-48Q depict various amino acid sequences of exemplary opsins, signal peptides, signal sequences, ER export sequences, and a trafficking sequence, as well as a polynucleotide sequence encoding Champ.

Figures 49A-49J depict tables and charts containing descriptions of at least some of the opsins described herein.

Figures 50-54 depict various aspects of embodiments of optical and/or electronic connectors in accordance with the present invention.

Figure 55 depicts one embodiment of a delivery segment and applicator configuration.

Figure 56 depicts an embodiment of a percutaneous feedthrough in accordance with the present invention.

Figures 57A-59 depict various aspects of embodiments of configurations of optical feedthroughs in accordance with the present invention.

Figures 60-62 depict various aspects of embodiments of light delivery configurations and related issues and data, which may be utilized for optogenetic treatment of a human in accordance with the present invention.

Figures 63A-64 depict various aspects of embodiments of light delivery strain relief configurations and related issues and data, which may be utilized for optogenetic treatment of a human in accordance with the present invention.

Figures 65-67 depict various aspects of embodiments of in-vivo light collection configurations and related issues and data, which may be utilized for optogenetic treatment of a human in accordance with the present invention.

Figure 68 depicts an embodiment for mounting an external charging device in accordance with the present invention.

Figures 69A-70 depict embodiments of an elongate member for use in the surgical implantation of optogenetic therapeutic devices in accordance with the present invention.

Figure 71 illustrates a configuration for modulating the activity certain aspects of motor function of the basal ganglia of the brain in accordance with the present invention.

Figures 72A-75 illustrate various configurations for conducting light-based therapeutic interventions to address motor disorders in the brain.

Figure 76 illustrates a system configuration for conducting light-based therapeutic interventions to address motor disorders in the brain.

Figure 77 illustrates a detailed schematic representation of a system configuration for conducting light-based therapeutic interventions to address motor disorders in the brain.

Figure 78 illustrates an action spectra pertinent to Arch-T and Chrimson opsin proteins.

Figures 79-84 illustrate sample results pertinent to an animal study wherein light-based therapeutic interventions have been utilized to address motor disorders in the brain.

DETAILED DESCRIPTION

Referring to Figure 1, from a high-level perspective, an optogenetics-based neuromodulation intervention involves determination of a desired nervous system functional modulation which can be facilitated by optogenetic excitation and/or inhibition (2), followed by a selection of neuroanatomic resource within the patient to provide such outcome (4), delivery of an effective amount of polynucleotide encoding a light-responsive opsin protein which is expressed in neurons of the targeted neuroanatomy (6), waiting for a period of time to ensure that sufficient portions of the targeted neuroanatomy will indeed express the light-responsive opsin protein-driven currents upon exposure to light (8), and delivering light to the targeted neuroanatomy to cause controlled, specific excitation and/or inhibition of such neuroanatomy by virtue of the presence of the light-responsive opsin protein therein (10) that may modulate the membrane potential of a neuron, or other cell by transporting ions through the membrane.

As noted above, an optogenetics-based neuromodulation intervention involves determination of a desired nervous system functional modulation which can be facilitated by optogenetic excitation and/or inhibition, followed by a selection of neuroanatomic resource within the patient to provide such outcome, delivery of an effective amount of polynucleotide encoding a light-responsive opsin protein which is expressed in neurons of the targeted neuroanatomy, waiting for a period of time to ensure that sufficient portions of the targeted neuroanatomy will indeed express the light-responsive opsin protein-driven currents upon exposure to light, and delivering light to the targeted neuroanatomy to cause controlled, specific

excitation and/or inhibition of such neuroanatomy by virtue of the presence of the light-responsive opsin protein therein.

While the development and use of transgenic animals has been utilized to address some of the aforementioned challenges, such techniques are not suitable in human medicine. Means to deliver the light-responsive opsin to cells in vivo are required; there are a number of potential methodologies that can be used to achieve this goal. These include viral mediated gene delivery, electroporation, optoporation, ultrasound, hydrodynamic delivery, or the introduction of naked DNA either by direct injection or complemented by additional facilitators such as cationic lipids or polymers.

Viral expression systems have the dual advantages of fast and versatile implementation combined with high copy number for robust expression levels in targeted neuroanatomy. Cellular specificity may be obtained with viruses by virtue of promoter selection if the promoters are small and specific, by localized targeting, and by restriction of opsin activation (i.e., via targeted illumination) of particular cells or projections of cells. In an embodiment, an opsin is targeted by methods described in Yizhar et al. 2011, Neuron 71:9-34. In addition, different serotypes of the virus (conferred by the viral capsid or coat proteins) will show different tissue tropism. Lenti- and adeno-associated ("AAV") viral vectors have been utilized successfully to introduce opsins into the mouse, rat and primate brain. Other vectors include but are not limited to equine infectious anemia virus pseudotyped with a retrograde transport protein (e.g., Rabies G protein), and herpes simplex virus ("HSV").

Additionally, these have been well tolerated and highly expressed over relatively long periods of time with no reported

adverse effects, providing the opportunity for long-term treatment paradigms. Lentivirus, for example, is easily produced using standard tissue culture and ultracentrifuge techniques, while AAV may be reliably produced either by individual laboratories or through core viral facilities. AAV is a preferred vector due to its safety profile, and AAV serotypes 1 and 6 have been shown to infect motor neurons following intramuscular injection in primates. Additionally, AAV serotype 2 has been shown to be expressed and well tolerated in human patients.

Viral expression techniques, generally comprising delivery of DNA encoding a desired opsin and promoter/catalyst sequence packaged within a recombinant viral vector have been utilized with success in mammals to effectively transfect targeted neuroanatomy and deliver genetic material to the nuclei of targeted neurons, thereby inducing such neurons to produce light-sensitive proteins which are migrated throughout the neuron cell membranes where they are made functionally available to illumination components of the interventional system. Typically a viral vector will package what may be referred to as an "opsin expression cassette", which will contain the opsin (e.g., ChR2, NpHR, Arch, etc.) and a promoter that will be selected to drive expression of the particular opsin within a targeted set of cells. In the case of adeno-associated virus (AAV), the gene of interest (opsin) can be in a single stranded configuration with only one opsin expression cassette or in a self-complementary structure with two copies of opsin expression cassette complementary in sequence with one another and connected by hairpin loops. The self-complementary AAVs are thought to be more stable and show higher expression levels and show faster expression. A various number of serotypes can be

used to express the gene of interest, with serotypes varying in their capsid proteins and tissue tropism. Potential AAV serotypes include, but are not limited to, AAV1, AAV2, AAV4, AAV5, AAV6, AAV7, AAV8, and AAV9. The promoter within the cassette may confer specificity to a targeted tissue, such as in the case of the human synapsin promoter ("hSyn") or the human Thy1 promoter ("hThy1"), which allow protein expression of the gene under its control in neurons. Alternatively, a ubiquitous promoter may be utilized, such as the human cytomegalovirus ("CMV") promoter, or the chicken beta-actin ("CBA") promoter, each of which is not neural specific, and each of which has been utilized safely in gene therapy trials for neurodegenerative disease. Another example is the human elongation factor-1 alpha promoter (EF1a), which also allows ubiquitous expression of the gene. Another example are the calmodulin-dependent protein kinase II promoters (e.g. CaMKii, CaMK2A, CaMK2B, CaMK2D, and/or CaMK2G), which allow for targeting of excitatory glutamatergic neurons. Viral constructs carrying opsins are optimized for specific cell populations and are not limited to such illustrative examples.

Delivery of the virus comprising the light-responsive opsin protein to be expressed in neurons of the targeted neuroanatomy may involve injection, infusion, or instillation in one or more configurations. By way of nonlimiting example, in a Parkinson's disease therapy configuration, delivery means may include tissue structure injection (or infusion) (i.e., directly into the STN and/or other targeted at brain structures and/or basal ganglia such as a SNr, a globus pallidus, and/or a striatum).

Tissue structures may be specifically targeted for viral injection. For example, it may be desirable to directly inject the STN, or other such targeted neuroanatomy. In such an

embodiment, after creating an access pathway, such as a cranial bore hole to allow stereotactic and laparoscopic tools (cannula, needle, tools, etc.) to approach the STN, an infusion cannula may be inserted into the STN or its neighboring regions. Alternatively access to the pertinent region of the basal ganglia may be gained by using a stereotactic surgical system such as the NextFrame and microTargeting Platforms from Medtronic that are routinely used in deep brain stimulation (DBS) implantation surgery. The infusion cannula may be guided into the pertinent anatomy using the same available stereotactic means and imaging tools, such as one or more cameras, ultrasound, fluoroscopy, or the like. The pertinent vector solution may be injected through the cannula where it may diffuse throughout the tissue and be taken up by the neural cell bodies. The vector solution may be injected as a single bolus dose, multiple injections throughout the tissue structure, or slowly through an infusion pump (1 to 100 uL/min). Considering that the STN is ellipsoidal and has an average size of 4mm x 5mm x 6mm with a corresponding average tissue volume of approximately 100 mm^3 efficient viral infection may be achieved using between 1-100 uL saline solution containing between approximately 1×10^8 to 1×10^{14} viral genomes of the desired vector. Alternately, this viral solution may be infused over multiple sites to more evenly disperse the vector within the STN. An infusion volume of between approximately 0.05 and 0.5 ul for each mm^3 of target tissue may be preferable. This corresponds to an infusion volume of approximately 22ul of viral solution. An infusion rate of between 0.1-10 ul/minute may be preferable.

After delivery of the gene to the targeted neuroanatomy, an expression time period generally is required to ensure that

sufficient portions of the targeted neuroanatomy will express the light-responsive opsin protein upon exposure to light. This waiting period may comprise a period of between about 2 weeks and 6 months. After this period of time, light may be delivered to the targeted neuroanatomy to facilitate the desired therapy. Such delivery of light may take the form of many different configurations, including transcutaneous configurations, implantable configurations, configurations with various illumination wavelengths, pulsing configurations, tissue interfaces, etc., as described below in further detail.

Referring to Figure 2, a suitable light delivery system comprises one or more applicators (A) configured to provide light output to the targeted tissue structures. The light may be generated within the applicator (A) structure itself, or within a housing (H) that is operatively coupled to the applicator (A) via one or more delivery segments (DS). The one or more delivery segments (DS) serve to transport, or guide, the light to the applicator (A) when the light is not generated in the applicator itself. The applicator and/or the delivery segment may be considered to be light delivery elements, or as an assembly forming a light delivery element. In the case where the light is produced in the applicator, that portion of the applicator between the light source and the target tissue may be considered to be a light delivery element. In an embodiment wherein the light is generated within the applicator (A), the delivery segment (DS) may simply comprise an electrical connector to provide power to the light source and/or other components which may be located distal to, or remote from, the housing (H). The one or more housings (H) preferably are configured to serve power to the light source and operate other electronic circuitry, including, for example, telemetry,

communication, control and charging subsystems. External programmer and/or controller (P/C) devices may be configured to be operatively coupled to the housing (H) from outside of the patient via a communications link (CL), which may be configured to facilitate wireless communication or telemetry, such as via transcutaneous inductive coil configurations, between the programmer and/or controller (P/C) devices and the housing (H). The programmer and/or controller (P/C) devices may comprise input/output (I/O) hardware and software, memory, programming interfaces, and the like, and may be at least partially operated by a microcontroller or processor (CPU), which may be housed within a personal computing system which may be a stand-alone system, or be configured to be operatively coupled to other computing or storage systems.

Referring to Figures 3A and 3B, as described above, various opsin protein configurations are available to provide excitatory and inhibitory functionality in response to light exposure at various wavelengths. Figure 3A (1000) depicts wavelength vs. activation for three different opsins; Figure 3B (1002) emphasizes that various opsins also have time domain activation signatures that may be utilized clinically; for example, certain step function opsins ("SFO") are known to have activations which last into the range of 30 minutes after stimulation with light.

Referring to Figure 3C (1004), a variety of light-emitting diodes (LED) are commercially available to provide illumination at relatively low power with various wavelengths. As described above in reference to Figure 2, in one embodiment, light may be generated within the housing (H) and transported to the applicator (A) via the delivery segment (DS). Light may also be produced at or within the applicator (A) in various

configurations. The delivery segments (DS) may consist of electrical leads or wires without light transmitting capability in such configurations. In other embodiments, light may be delivered using the delivery segments (DS) to be delivered to the subject tissue structures at the point of the applicator (A), or at one or more points along the deliver segment (DS) itself (for example, in one case the DS may be a fiber laser). Referring again to Figure 3C (1004), an LED (or alternatively, "ILED", to denote the distinction between this inorganic system and Organic LEDs) typically is a semiconductor light source, and versions are available with emissions across the visible, ultraviolet, and infrared wavelengths, with relatively high brightness. When a light-emitting diode is forward-biased (switched on), electrons are able to recombine with electron holes within the device, releasing energy in the form of photons. This effect is called electroluminescence and the color of the light (corresponding to the energy of the photon) is determined by the energy gap of the semiconductor. An LED is often small in area (less than 1 mm^2), and integrated optical components may be used to shape its radiation pattern. In one embodiment, for example, an LED variation manufactured by Cree Inc. and comprising a Silicon Carbide device providing 24mW at 20mA may be utilized as an illumination source.

Organic LEDs (or "OLED"s) are light-emitting diodes wherein the emissive electroluminescent layer is a film of organic compound that emits light in response to an electric current. This layer of organic semiconductor material is situated between two electrodes, which can be made to be flexible. At least one of these electrodes may be made to be transparent. The nontransparent electrode may be made to serve as a reflective layer along the outer surface on an optical applicator, as will

be explained later. The inherent flexibility of OLEDs provides for their use in optical applicators such as those described herein that conform to their targets or are coupled to flexible or movable substrates, as described in further detail below. It should be noted, however, due to their relatively low thermal conductivity, OLEDs typically emit less light per area than an inorganic LED.

Other suitable light sources for embodiments of the inventive systems described herein include polymer LEDs, quantum dots, light-emitting electrochemical cells, laser diodes, vertical cavity surface-emitting lasers, and horizontal cavity surface-emitting lasers.

Polymer LEDs (or "PLED"s), and also light-emitting polymers ("LEP"), involve an electroluminescent conductive polymer that emits light when connected to an external voltage. They are used as a thin film for full-spectrum color displays. Polymer OLEDs are quite efficient and require a relatively small amount of power for the amount of light produced.

Quantum dots (or "QD") are semiconductor nanocrystals that possess unique optical properties. Their emission color may be tuned from the visible throughout the infrared spectrum. They are constructed in a manner similar to that of OLEDs.

A light-emitting electrochemical cell ("LEC" or "LEEC") is a solid-state device that generates light from an electric current (electroluminescence). LECs may be usually composed of two electrodes connected by (e.g. "sandwiching") an organic semiconductor containing mobile ions. Aside from the mobile ions, their structure is very similar to that of an OLED. LECs have most of the advantages of OLEDs, as well as a few additional ones, including:

- The device does not depend on the difference in work function of the electrodes. Consequently, the electrodes can be made of the same material (e.g., gold). Similarly, the device can still be operated at low voltages;
- Recently developed materials such as graphene or a blend of carbon nanotubes and polymers have been used as electrodes, eliminating the need for using indium tin oxide for a transparent electrode;
- The thickness of the active electroluminescent layer is not critical for the device to operate, and LECs may be printed with relatively inexpensive printing processes (where control over film thicknesses can be difficult).

Semiconductor Lasers are available in a variety of output colors, or wavelengths. There are a variety of different configurations available that lend themselves to usage in the present invention, as well. Indium gallium nitride ($In_xGa_{1-x}N$, or just InGaN) laser diodes have high brightness output at both 405, 445, and 485 nm, which are suitable for the activation of ChR2. The emitted wavelength, dependent on the material's band gap, can be controlled by the GaN/InN ratio; violet-blue 420 nm for 0.2In/0.8Ga, and blue 440 nm for 0.3In/0.7Ga, to red for higher ratios and also by the thickness of the InGaN layers which are typically in the range of 2-3 nm.

A laser diode (or "LD") is a laser whose active medium is a semiconductor similar to that found in a light-emitting diode. The most common type of laser diode is formed from a p-n junction and powered by injected electric current. The former devices are sometimes referred to as injection laser diodes to distinguish them from optically pumped laser diodes. A laser diode may be formed by doping a very thin layer on the surface of a crystal wafer. The crystal may be doped to produce an n-

type region and a p-type region, one above the other, resulting in a p-n junction, or diode. Laser diodes form a subset of the larger classification of semiconductor p-n junction diodes. Forward electrical bias across the laser diode causes the two species of charge carrier - holes and electrons - to be "injected" from opposite sides of the p-n junction into the depletion region. Holes are injected from the p-doped, and electrons from the n-doped, semiconductor. A depletion region, devoid of any charge carriers, forms as a result of the difference in electrical potential between n- and p-type semiconductors wherever they are in physical contact. Due to the use of charge injection in powering most diode lasers, this class of lasers is sometimes termed "injection lasers" or "injection laser diodes" ("ILD"). As diode lasers are semiconductor devices, they may also be classified as semiconductor lasers. Either designation distinguishes diode lasers from solid-state lasers. Another method of powering some diode lasers is the use of optical pumping. Optically Pumped Semiconductor Lasers (or "OPSL") use a III-V semiconductor chip as the gain media, and another laser (often another diode laser) as the pump source. OPSLs offer several advantages over ILDs, particularly in wavelength selection and lack of interference from internal electrode structures. When an electron and a hole are present in the same region, they may recombine or "annihilate" with the result being spontaneous emission – i.e., the electron may re-occupy the energy state of the hole, emitting a photon with energy equal to the difference between the electron and hole states involved. (In a conventional semiconductor junction diode, the energy released from the recombination of electrons and holes is carried away as phonons, i.e., lattice vibrations, rather than as photons.) Spontaneous

emission gives the laser diode below lasing threshold similar properties to an LED. Spontaneous emission is necessary to initiate laser oscillation, but it is one among several sources of inefficiency once the laser is oscillating. The difference between the photon-emitting semiconductor laser and conventional phonon-emitting (non-light-emitting) semiconductor junction diodes lies in the use of a different type of semiconductor, one whose physical and atomic structure confers the possibility for photon emission. These photon-emitting semiconductors are the so-called "direct bandgap" semiconductors. The properties of silicon and germanium, which are single-element semiconductors, have bandgaps that do not align in the way needed to allow photon emission and are not considered "direct." Other materials, the so-called compound semiconductors, have virtually identical crystalline structures as silicon or germanium but use alternating arrangements of two different atomic species in a checkerboard-like pattern to break the symmetry. The transition between the materials in the alternating pattern creates the critical "direct bandgap" property. Gallium arsenide, indium phosphide, gallium antimonide, and gallium nitride are all examples of compound semiconductor materials that may be used to create junction diodes that emit light.

Vertical-cavity surface-emitting lasers (or "VCSEL"s) have the optical cavity axis along the direction of current flow rather than perpendicular to the current flow as in conventional laser diodes. With such a configuration, the active region length is very short compared with the lateral dimensions so that the radiation emerges from the surface of the cavity rather than from its edge. The reflectors at the ends of the cavity are dielectric mirrors made from alternating high and low

refractive index quarter-wave thick multilayer. VCSELs allow for monolithic optical structures to be produced.

Horizontal cavity surface-emitting lasers (or "HCSEL"s) combine the power and high reliability of a standard edge-emitting laser diode with the low cost and ease of packaging of a vertical cavity surface-emitting laser (VCSEL). They also lend themselves to use in integrated on-chip optronic, or photonic packages.

The irradiance required at the neural membrane in which the optogenetic channels reside is on the order of 0.05-2mW/mm^2 and depends upon numerous elements, such as opsin channel expression density, activation threshold, etc. A modified halorhodopsin resident within a neuron may be activated by illumination of the neuron with green or yellow light having a wavelength of between about 520nm and about 600nm, and in one example about 589nm, with an intensity of between about 0.5mW/mm^2 and about 10mW/mm^2, such as between about 1mW/mm^2 and about 5mW/mm^2, and in one example about 2.4mW/mm^2. Although the excitation spectrum may be different, similar exposure values hold for other opsins as well. For example, an "inhibitory" channel (such as those referred to as "iChR" or "SwiChR") may be utilized to open and permit large amounts of Cl- ions to pass, thereby hyperpolarizing the neuron more effectively and thus inhibiting the cell with efficiency and sensitivity. These opsins have action spectra similar to that of ChR and ChR2, with a peak response at about 460nm. Irradiance levels similar to those described for the inhibitory pumps may also be used to activate these channels. However, the duty cycles of the exposure may be much lower than those for activating ion pumps may be used because the channel lifetime is long, and allows multiple ions to transported per photon absorbed. Resetting (closing) an

inhibitory channel may achieved using red light in the wavelength range of 580-650nm and an intensity of between about 0.05mW/mm^2 and about 10mW/mm^2. Because most opsin-expressing targets are contained within a tissue or other structure, the light emitted from the applicator may need to be higher in order to attain the requisite values at the target itself. Light intensity, or irradiance, is lost predominantly due to optical scattering in tissue, which is a turbid medium. There is also parasitic absorption of endogenous chromophores, such as blood, that may also diminish the target exposure. Because of these effects, the irradiance range required at the output of an applicator is, for most of the cases described herein, between 1 - 100mW/mm^2. Referring to Figure 4, experiments have shown, for example, that for the single-sided exposure of illumination (I) from an optical fiber (OF) of a 1mm diameter nerve bundle (N), the measured response (in arbitrary units) vs. irradiance (or Light Power Density, in mW/mm^2) is asymptotic, as shown in the graph depicted in Figure 5 (1006). There is no appreciable improvement beyond 20mW/mm^2 for this specific configuration of opsin protein, expression density, illumination geometry, and pulse parameters. However, we may use this result to scale the irradiance requirements to other targets with similar optical properties and opsin protein expression densities. The data in Figure 5 (1006) may be used in a diffusion approximation optical model for neural materials, where the irradiance (I) obeys the following relation, $I=I_0e^{-(Q\mu z)}$. The resulting expression fits well with the following experimental data, and the result of this is given in the plot of Figure 6 (1008). The details are further discussed below.

The optical penetration depth, δ, is the tissue thickness that causes light to attenuate to e^{-1} (~37%) of its initial value, and is given by the following diffusion approximation.

$$\delta \approx \frac{1}{\sqrt{3\mu_a\mu_s'}},$$

where μ_a is the absorption coefficient, and μ_s' is the reduced scattering coefficient. The reduced scattering coefficient is a lumped property incorporating the scattering coefficient μ_s and the anisotropy g: $\mu_s' = \mu_s(1 - g)$ [cm^{-1}]. The purpose of μ_s' is to describe the diffusion of photons in a random walk of step size of $1/\mu_s'$ [cm] where each step involves isotropic scattering. Such a description is equivalent to description of photon movement using many small steps $1/\mu_s$ that each involve only a partial deflection angle θ, if there are many scattering events before an absorption event, i.e., $\mu_a << \mu_s'$. The anisotropy of scattering, g, is effectively the expectation value of the scattering angle, θ. Furthermore, μ_{eff} is a lumped parameter containing ensemble information regarding the absorption and scattering of materials, μ_{eff} = Sqrt($3\mu_a(\mu_a+\mu_s')$). The cerebral cortex constitutes a superficial layer of grey matter (high proportion of nerve cell bodies) and internally the white matter, which is responsible for communication between axons. The white matter appears white because of the multiple layers formed by the myelin sheaths around the axons, which are the origin of the high, inhomogeneous and anisotropic scattering properties of brain, and is a suitable surrogate for use in neural tissue optics calculations with published optical properties.

As was described earlier, the one-dimensional irradiance profile in tissue, I, obeys the following relation, $I=I_0e^{-(Q\mu z)}$,

where Q is the volume fraction of the characterized material that is surrounded by an optically neutral substance such as interstitial fluid or physiologic saline. In the case of most nerves, Q=0.45 can be estimated from cross-sectional images. The optical transport properties of tissue yield an exponential decrease of the irradiance (ignoring temporal spreading, which is inconsequential for this application) through the target, or the tissue surrounding the target(s). The plot described above in reference to Figure 6 illustrates good agreement between theory and model, validating the approach. It can be also seen that the optical penetration depth, as calculated by the above optical parameters agrees reasonably well with the experimental observations of measured response vs. irradiance for the example described above.

Furthermore, the use of multidirectional illumination, as has been described herein, may serve to reduce this demand, and thus the target radius may be considered as the limiting geometry, and not the diameter. For instance, if the abovementioned case of illuminating a 1mm nerve from 2 opposing sides instead of just the one, we can see that we will only need an irradiance of ~6mW/mm^2 because the effective thickness of the target tissue is now 1/2 of what it was. It should be noted that this is not a simple linear system, or the irradiance value would have been 20/2= 10mW/mm^2. The discrepancy lies in the exponential nature of the photon transport process, which yields the severe diminution of the incident power at the extremes of the irradiation field. Thus, there is a practical limit to the number of illumination directions that provide an efficiency advantage for deep, thick, and/or embedded tissue targets.

By way of non-limiting example, a 2mm diameter nerve target may be considered a 1mm thick target when illuminated

circumferentially. The effective diameter of the vagus nerve in the neck between about 1.5 and about 3 millimeters. Circumferential, and/or broad illumination may be employed to achieve electrically and optically efficient optogenetic target activation for larger structures and/or enclosed targets that cannot be addressed directly. This is illustrated in Figure 7, where Optical Fibers OF1 and OF2 now illuminate the targeted tissue structure (N) from diametrically opposing sides with Illumination Fields I1 and I2, respectively. Alternately, the physical length of the illumination may be extended to provide for more photoactivation of expressed opsin proteins, without the commensurate heat buildup associated with intense illumination limited to smaller area. That is, the energy may be spread out over a larger area to reduce localized temperature rises. In a further embodiment, the applicator may contain a temperature sensor, such as a resistance temperature detector (RTD), thermocouple, or thermistor, etc. to provide feedback to the processor in the housing to assure that temperature rises are not excessive, as is discussed in further detail below.

From the examples above, activation of a neuron, or set(s) of neurons within a 2.5mm diameter vagus nerve may be nominally circumferentially illuminated by means of the optical applicators described later using an external surface irradiance of $\geq 5.3 mW/mm^2$, as can be seen using the curve described above in reference to Figure 6 when considering the radius as the target tissue thickness, as before. However, this is greatly improved over the $28 mW/mm^2$ required for a 2.5mm target diameter, or thickness. In this case, 2 sets of the opposing illumination systems from the embodiment above may be used, as the target surface area has increased, configuring the system to use Optical Fibers OF3 and OF4 to provide Illumination Fields I3 and

I4, as shown in Figure 8. There are also thermal concerns to be understood and accounted for in the design of optogenetic systems, and excessive irradiances will cause proportionately large temperature rises. Thus, it may be beneficial to provide more direct optical access to targets embedded in tissues with effective depths of greater than ~2mm because of the regulatory limit applied to temperature rise allowed by conventional electrical stimulation, or "e-stim", devices of deltaT≤2.0°C.

As described above, optical applicators suitable for use with the present invention may be configured in a variety of ways. Referring to Figures 9A-9C, a helical applicator with a spring-like geometry is depicted. Such a configuration may be configured to readily bend with, and/or conform to, a targeted tissue structure (N), such as a nerve, nerve bundle, vessel, or other structure to which it is temporarily or permanently coupled. Such a configuration may be coupled to such targeted tissue structure (N) by "screwing" the structure onto the target, or onto one or more tissue structures which surround or are coupled to the target. As shown in the embodiment of Figure 9A, a waveguide may be connected to, or be a contiguous part of, a delivery segment (DS), and separable from the applicator (A) in that it may be connected to the applicator via connector (C). Alternately, it may be affixed to the applicator portion without a connector and not removable. Both of these embodiments are also described with respect to the surgical procedure described herein. Connector (C) may be configured to serve as a slip-fit sleeve into which both the distal end of delivery segment (DS) and the proximal end of the applicator are inserted. In the case where the delivery segment is an optical conduit, such an optical fiber, it preferably should be somewhat undersized in comparison to the applicator waveguide to allow for axial

misalignment. For example, a 50µm core diameter fiber may be used as delivery segment (DS) to couple to a 100µm diameter waveguide in the applicator (A). Such 50µm axial tolerances are well within the capability of modern manufacturing practices, including both machining and molding processes. The term waveguide is used herein to describe an optical conduit that confines light to propagate nominally within it, albeit with exceptions for output coupling of the light, especially to illuminate the target.

Figure 50 shows an exemplary embodiment, wherein Connector C may comprise a single flexible component made of a polymer material to allow it to fit snugly over the substantially round cross-sectional Delivery Segment DS1, and Applicator A. These may be waveguides such as optical fibers and similar mating structures on the applicator, and/or delivery segment, and/or housing to create a substantially water-tight seal, shown as SEAL1 & SEAL2, that substantially prevents cells, tissues, fluids, and/or other biological materials from entering the Optical Interface (O-INT).

Figure 51 shows an alternate exemplary embodiment, wherein Connector C may comprise a set of seals, shown as SEAL0 through SEAL4, rather than rely upon the entire device to seal the optical connection. A variety of different sealing mechanisms may be utilized, such as, by way of non-limiting example, o-rings, single and dual lip seals, and wiper seals. The materials that may be used, by way of non-limiting example, are Nitrile (NBR, such as S1037), Viton, Silicone (VMQ, such as V1039, S1083 and S1146), Neoprene, Chloroprene (CR), Ethylene Propylene (EPDM, such as E1074 and E1080), Polyacrylic (ACM), Styrene Butadiene Rubber (SBR), and Fluorosilicone (FVMQ).

SEAL0 through SEAL4 are shown in the exemplary embodiment to be resident within a Seal Bushing SB.

Alternately, the seal may be a component of the delivery segment and/or the housing, and/or the applicator, thus eliminating one insertion seal with a fixed seal, which may improve the robustness of the system. Such a hybrid system is shown in Figure 52, where SEAL1 is shown as an integral seal permanently linking Applicator A with its subcomponent Connector C such that the connection at Optical Interface O-INT is established by inserting Delivery Segment DS1 into Connector C, and having seals SEAL2, SEAL3, and SEAL4 create the substantially water-tight seal about Delivery Segment DS1, while SEAL1 is integrated into Connector C.

Alternately, or in addition to the other embodiments, a biocompatible adhesive, such as, by way of non-limiting example, Loctite 4601, may be used to adhere the components being connected. Although other adhesives are considered within the scope of the present invention, cyanoacrylates such as Loctite 4601, have relatively low shear strength, and may be overcome by stretching and separating the flexible sleeve from the mated components for replacement without undue risk of patient harm. However, care must be taken to maintain clarity at Optical Interface O-INT.

Figure 53 shows an alternate exemplary embodiment, wherein Connector C may further comprise a high precision sleeve, Split Sleeve SSL, which is configured to axially align the optical elements at Optical Interface O-INT. By way of non-limiting example, split zirconia ceramic sleeves for coupling both Ø1.25 and Ø2.5mm fiber optic ferrules, not shown, may be used to provide precision centration and all those components are available from Adamant-Kogyo. Similarly, other diameters may be

accommodated using the same split sleeve approach to butt-coupling optical elements, such as optical fibers themselves.

Figure 54 shows an alternate exemplary embodiment, wherein the seals of Figures 52-53 of Connector C have been replaced by an integral sealing mechanism comprised of seals SEAL2 through SEAL4, that serve to fit about the circumference of Delivery Segment DS1, and create gaps GAP1 and GAP2. Rather than utilizing separate sealing elements, the sealing elements as shown are made to be part of an integrated sleeve.

Alternately, although not shown, the sealing mechanism may be configured to utilize a threaded mechanism to apply axial pressure to the sealing elements to create a substantially water-tight seal that substantially prevents cells, tissues, fluids, and/or other biological materials from entering the optical interfaces.

As shown in Figures 9A-9C and 50-54, the optical elements being connected by Connector C may be optical fibers, as shown in the exemplary embodiments. They may also be other portions of the therapeutic system, such as the delivery segments, an optical output from the housing, and an applicator itself.

Biocompatible adhesive may be applied to the ends of connector (C) to ensure the integrity of the coupling. Alternately, connector (C) may be configured to be a contiguous part of either the applicator or the delivery device. Connector (C) may also provide a hermetic electrical connection in the case where the light source is located at the applicator. In this case, it may also serve to house the light source. The light source may be made to butt-couple to the waveguide of the applicator for efficient optical transport. Connector (C) may be contiguous with the delivery segment or the applicator. Connector (C) may be made to have cross-sectional shape with

multiple internal lobes such that it may better serve to center the delivery segment to the applicator.

The applicator (A) in this embodiment also comprises a Proximal Junction (PJ) that defines the beginning of the applicator segment that is in optical proximity to the target nerve. That is, PJ is the proximal location on the applicator optical conduit (with respect to the direction the light travels into the applicator) that is well positioned and suited to provide for light output onto the target. The segment just before PJ is curved, in this example, to provide for a more linear aspect to the overall device, such as might be required when the applicator is deployed along a nerve, and is not necessarily well suited for target illumination. Furthermore, the applicator of this exemplary embodiment also comprises a Distal Junction (DJ), and Inner Surface (IS), and an Outer Surface (OS). Distal Junction (DJ) represents the final location of the applicator still well positioned and suited to illuminate the target tissue(s). However, the applicator may extend beyond DJ, no illumination is intended beyond DJ. DJ may also be made to be a reflective element, such as a mirror, retro-reflector, diffuse reflector, a diffraction grating, A Fiber Bragg Grating ("FBG" - further described below in reference to Figure 11), or any combination thereof. An integrating sphere made from an encapsulated "bleb" of $BaSO_4$, or other such inert, non-chromophoric compound may serve a diffuse reflector when positioned, for example, at the distal and of the applicator waveguide. Such a scattering element should also be placed away from the target area, unless light that is disallowed from waveguiding due to its spatial and/or angular distribution is desired for therapeutic illumination.

Inner Surface (IS) describes the portion of the applicator that "faces" the target tissue, shown, for example, in Figure 9B as Nerve (N). That is, N lies within the coils of the applicator and is in optical communication with IS. That is, light exiting IS is directed towards N. Similarly, Outer Surface (OS) describes that portion of the applicator that is not in optical communication with the target. That is, the portion that faces outwards, away from the target, such a nerve that lies within the helix. Outer Surface (OS) may be made to be a reflective surface, and as such will serve to confine the light within the waveguide and allow for output to the target via Inner Surface (IS). The reflectivity of OS may be achieved by use of a metallic or dielectric reflector deposited along it, or simply via the intrinsic mechanism underlying fiber optics, total internal reflection ("TIR"). Furthermore, Inner Surface (IS) may be conditioned, or affected, such that it provides for output coupling of the light confined within the helical waveguide. The term output coupling is used herein to describe the process of allowing light to exit the waveguide in a controlled fashion, or desired manner. Output coupling may be achieved in various ways. One such approach may be to texture IS such that light being internally reflected no longer encounters a smooth TIR interface. This may be done along IS continuously, or in steps. The former is illustrated in Figure 10A in a schematic representation of such a textured applicator, as seen from IS. Surface texture is synonymous with surface roughness, or rugosity. It is shown in the embodiment of Figure 10A as being isotropic, and thus lacking a definitive directionality. The degree of roughness is proportional to the output coupling efficiency, or the amount of light removed from the applicator in proportion to the amount of light encountering

the Textured Area. In one embodiment, the configuration may be envisioned as being akin to what is known as a "matte finish", whereas OS will may be configured to have a more planar and smooth finish, akin to what is known as a "gloss finish". A Textured Area may be an area along or within a waveguide that is more than a simple surface treatment. It might also comprise a depth component that either diminishes the waveguide cross sectional area, or increases it to allow for output coupling of light for target illumination.

In this non-limiting example, IS contains areas textured with Textured Areas TA correspond to output couplers (OCs), and between them are Untextured Areas (UA). Texturing of textured Areas (TA) may be accomplished by, for example, mechanical means (such as abrasion) or chemical means (such as etching). In the case where optical fiber is used as the basis for the applicator, one may first strip buffer and cladding layers which may be coupled to the core, to expose the core for texturing. The waveguide may lay flat (with respect to gravity) for more uniform depth of surface etching, or may be tilted to provide for a more wedge-shaped etch.

Referring to the schematic representation of Figure 10B, an applicator is seen from the side with IS facing downward, and TA that do not wrap around the applicator to the outer surface (OS). Indeed, in such embodiment, they need not wrap even halfway around: because the texture may output couple light into a broad solid angle, Textured Areas (TA) need not be of large radial angular extent.

In either case, the proportion of light coupled out to the target also may be controlled to be a function of the location along the applicator to provide more uniform illumination output coupling from IS to the target, as shown in Figures 10A-11 and

20-23. This may be done to account for the diminishing proportion of light encountering later (or distal) output coupling zones. For example, if we consider the three output coupling zones represented by Textured Areas (TA) in the present non-limiting example schematically illustrated in Figure 10B, we now have TA1, TA2, and TA3. In order to provide equal distribution of the output coupled energy (or power) the output coupling efficiencies would be as follows: TA1 = 33%, TA2=50%, TA3=100%. Of course, other such portioning schemes may be used for different numbers of output coupling zones TAx, or in the case where there is directionality to the output coupling efficiency and a retro-reflector is used in a two-pass configuration, as is described in further detail below.

Referring to Figure 10C, in the depicted alternate embodiment, distal junction (DJ) is identified to make clear the distinction of the size of TA with respect to the direction of light propagation.

In another embodiment, as illustrated in Figure 10D, Textured Areas TA1, TA2 and TA3 are of increasing size because they are progressively more distal with the applicator. Likewise, Untextured Areas UA1, UA2 and UA3 are shown to become progressively smaller, although they also may be made constant. The extent (or separation, size, area, etc.) of the Untextured Areas (UAx) dictates the amount of illumination zone overlap, which is another means by which the ultimate illumination distribution may be controlled and made to be more homogeneous in ensemble. Note that Outer Surface (OS) may be made to be reflective, as described earlier, to prevent light scattered from a TA to escape the waveguide via OS and enhance the overall efficiency of the device. A coating may be used for the reflective element. Such coating might be, for example,

metallic coatings, such as, Gold, Silver, Rhodium, Platinum, Aluminum. Alternately, a diffusive coating of a non-chromophoric substance, such as, but not limited to, $BaSO_4$ may be used as a diffuse reflector.

In a similar manner, the surface roughness of the Textured Areas (TA) may be changed as a function of location along the applicator. As described above, the amount of output coupling is proportional to the surface rugosity, or roughness. In particular, it is proportional to the first raw moment ("mean") of the distribution characterizing the surface rugosity. The uniformity in both its spatial and angular emission are proportional to the third and fourth standardized moments (or "skewness" and "kurtosis"), respectively. These are values that may be adjusted, or tailored, to suit the clinical and/or design need in a particular embodiment. Also, the size, extent, spacing and surface roughness may each be employed for controlling the amount and ensemble distribution of the target illumination.

Alternately, directionally specific output coupling may be employed that preferentially outputs light traveling in a certain direction by virtue of the angle it makes with respect to IS. For example, a wedge-shaped groove transverse to the waveguide axis of IS will preferentially couple light encountering it when the angle incidence is greater than that required for TIR. If not, the light will be internally reflected and continue to travel down the applicator waveguide.

Furthermore, in such a directionally specific output coupling configuration, the applicator may utilize the abovementioned retro-reflection means distal to DJ. Figure 11 illustrates an example comprising a FBG retro-reflector.

A waveguide, such as a fiber, can support one or even many guided modes. Modes are the intensity distributions that are located at or immediately around the fiber core, although some of the intensity may propagate within the fiber cladding. In addition, there is a multitude of cladding modes, which are not restricted to the core region. The optical power in cladding modes is usually lost after some moderate distance of propagation, but can in some cases propagate over longer distances. Outside the cladding, there is typically a protective polymer coating, which gives the fiber improved mechanical strength and protection against moisture, and also determines the losses for cladding modes. Such buffer coatings may consist of acrylate, silicone or polyimide. For long-term implantation in a body, it may be desirable to keep moisture away from the waveguide to prevent refractive index changes that will alter the target illumination distribution and yield other commensurate losses. Therefore, for long-term implantation, a buffer layer (or region) may be applied to the Textured Areas TAx of the applicator waveguide. In one embodiment, "long-term" may be defined as greater than or equal to 2 years. The predominant deleterious effect of moisture absorption on optical waveguides is the creation of hydroxyl absorption bands that cause transmission losses in the system. This is a negligible for the visible spectrum, but an issue for light with wavelengths longer than about 850nm. Secondarily, moisture absorption may reduce the material strength of the waveguide itself and lead to fatigue failure. Thus, while moisture absorption is a concern, in certain embodiments it is more of a concern for the delivery segments, which are more likely to undergo more motion and cycles of motion than the applicator.

Furthermore, the applicator may be enveloped or partially enclosed by a jacket, such as Sleeve S shown in Figure 9B. Sleeve S may be made to be a reflector, as well, and serve to confine light to the intended target. Reflective material(s), such as Mylar, metal foils, or sheets of multilayer dielectric thin films may be located within the bulk of Sleeve S, or along its inner or outer surfaces. While the outer surface of Sleeve S also may be utilized for reflective purposes, in certain embodiments such a configuration is not preferred, as it is in more intimate contact with the surrounding tissue than the inner surface. Such a jacket may be fabricated from polymeric material to provide the necessary compliance required for a tight fit around the applicator. Sleeve S, or an adjunct or alternative to, may be configured such that its ends slightly compress the target over a slight distance, but circumferentially to prevent axial migration, infiltration along the target surface. Sleeve S may also be made to be highly scattering (white, high albedo) to serve as diffusive retro-reflector to improve overall optical efficiency by redirecting light to the target.

Fluidic compression may also be used to engage the sleeve over the applicator and provide for a tighter fit to inhibit proliferation of cells and tissue ingrowth that may degrade the optical delivery to the target. Fluidic channels may be integrated into Sleeve S and filled at the time of implantation. A valve or pinch-off may be employed to seal the fluidic channels. Further details are described herein.

Furthermore, Sleeve S may also be made to elute compounds that inhibit scar tissue formation. This may provide for increased longevity of the optical irradiation parameters that might otherwise be altered by the formation of a scar, or the

infiltration of tissue between the applicator and the target. Such tissue may scatter light and diminish the optical exposure. However, the presence of such infiltrates could also be detected by means of an optical sensor placed adjacent to the target or the applicator. Such a sensor could serve to monitor the optical properties of the local environment for system diagnostic purposes. Sleeve S may also be configured to utilize a joining means that is self-sufficient, such as is illustrated in the cross-section of Figure 9C, wherein at least a part of the applicator is shown enclosed in cross-section AA. Alternately, Sleeve S may be joined using sutures or such mechanical or geometric means of attachment, as illustrated by element F in the simplified schematic of Figure 9C.

In a further embodiment, output coupling may be achieved by means of localized strain-induced effects with the applicator waveguide that serve to alter the trajectory of the light within it, or the bulk refractive index on the waveguide material itself, such as the use of polarization or modal dispersion. For example, output coupling may be achieved by placing regions (or areas, or volumes) of form-induced refractive index variation and/or birefringence that serve to alter the trajectory of the light within the waveguide beyond the critical angle required for spatial confinement and/or by altering the value of the critical angle, which is refractive-index-dependent. Alternately, the shape of the waveguide may be altered to output couple light from the waveguide because the angle of incidence at the periphery of the waveguide has been modified to be greater than that of the critical angle required for waveguide confinement. These modifications may be accomplished by transiently heating, and/or twisting, and/or pinching the applicator in those regions where output coupling

for target illumination is desired. A non-limiting example is shown in Figure 13, where a truncated section of Waveguide WG has been modified between Endpoints (EP) and Centerpoint (CP). The cross-sectional area and/or diameter of CP<EP. Light propagating through Waveguide WG will encounter a higher angle of incidence at the periphery of the waveguide due to the mechanical alteration of the waveguide material, resulting in light output coupling near CP in this exemplary configuration. It should be noted that light impinging upon the relatively slanted surface provided by the taper between EP and CP may output couple directly from the WG when the angle is sufficiently steep, and may require more than a single interaction with said taper before its direction is altered to such a degree that is ejected from the WG. As such, consideration may be given to which side of the WG is tapered, if it is not tapered uniformly, such that the output coupled light exiting the waveguide is directed toward the target, or incident upon an alternate structure, such as a reflector to redirect it to the target.

Referring to Figure 12 and the description that follows, for contextual purposes an exemplary scenario is described wherein a light ray is incident from a medium of refractive index "n" upon a core of index "n_{core}" at a maximum acceptance angle, $Theta_{max}$, with Snell's law at the medium-core interface being applied. From the geometry illustrated in Figure 12, we have:

$$\sin\theta_r = \sin(90^\circ - \theta_c) = \cos\theta_c$$

where

$$\theta_c = \sin^{-1} \frac{n_{clad}}{n_{core}}$$

is the critical angle for total internal reflection.

Substituting cos θ_c for sin θ_r in Snell's law we get:

$$\frac{n}{n_{core}} \sin \theta_{max} = \cos \theta_c.$$

By squaring both sides we get:

$$\frac{n^2}{n_{core}^2} \sin^2 \theta_{max} = \cos^2 \theta_c = 1 - \sin^2 \theta_c = 1 - \frac{n_{clad}^2}{n_{core}^2}.$$

Solving, we find the formula stated above:

$$n\sin\theta_{max} = \sqrt{n_{core}^2 - n_{clad}^2},$$

This has the same form as the numerical aperture (NA) in other optical systems, so it has become common to define the NA of any type of fiber to be

$$NA = \sqrt{n_{core}^2 - n_{clad}^2}.$$

It should be noted that not all of the optical energy impinging at less than the critical angle will be coupled out of the system.

Alternately, the refractive index may be modified using exposure to ultraviolet (UV) light, such might be done to create a Fiber Bragg Grating (FBG). This modification of the bulk waveguide material will cause the light propagating through the waveguide to refractive to greater or lesser extent due to the refractive index variation. Normally a germanium-doped silica fiber is used in the fabrication of such refractive index variations. The germanium-doped fiber is photosensitive, which means that the refractive index of the core changes with exposure to UV light.

Alternately, and/or in combination with the abovementioned aspects and embodiments of the present invention, "whispering

gallery modes" may be utilized within the waveguide to provide for enhanced geometric and/or strain-induced output coupling of the light along the length of the waveguide. Such modes of propagation are more sensitive to small changes in the refractive index, birefringence and the critical confinement angle than typical waveguide-filling modes because they are concentrated about the periphery of a waveguide. Thus, they are more susceptible to such means of output coupling and provide for more subtle means of producing a controlled illumination distribution at the target tissue.

Alternately, more than a single Delivery Segment DS may be brought from the housing (H) to the applicator (A), as shown in Figure 14. Here Delivery Segments DS1 and DS2 are separate and distinct. They may carry light from different sources (and of different color, or wavelength, or spectra) in the case where the light is created in housing (H), or they may be separate wires (or leads, or cables) in the case where the light is created at or near applicator (A).

In either case, the applicator may alternately further comprise separate optical channels for the light from the different Delivery Segments DSx (where x denotes the individual number of a particular delivery segment) in order to nominally illuminate the target area. A further alternate embodiment may exploit the inherent spectral sensitivity of the retro-reflection means to provide for decreased output coupling of one channel over another. Such would be the case when using a FBG retro-reflector, for instance. In this exemplary case, light of a single color, or narrow range of colors will be acted on by the FBG. Thus, it will retro-reflect only the light from a given source for bi-directional output coupling, while light from the other source will pass through largely unperturbed and

be ejected elsewhere. Alternately, a chirped FBG may be used to provide for retro-reflection of a broader spectrum, allowing for more than a single narrow wavelength range to be acted upon by the FBG and be utilized in bi-directional output coupling. Of course, more than two such channels and/or Delivery Segments (DSx) are also within the scope of the present invention, such as might be the case when selecting to control the directionality of the instigated nerve impulse, as will be described in a subsequent section.

Alternately, multiple Delivery Segments may also provide light to a single applicator, or become the applicator(s) themselves, as is described in further detail below. For example, a single optical fiber deployed to the targeted tissue structure, wherein the illumination is achieved through the end face of the fiber is such a configuration, albeit a simple one. In this configuration, the end face of the fiber is the output coupler, or, equivalently, the emission facet, as the terms are interchangeable as described herein.

Alternately, a single delivery device may be used to channel light from multiple light sources to the applicator. This may be achieved through the use of spliced, or conjoined, waveguides (such as optical fibers), or by means of a fiber switcher, or a beam combiner prior to initial injection into the waveguide, as shown in Figure 15.

In this embodiment, Light Sources LS1 and LS2 output light along paths W1 and W2, respectively. Lenses L1 and L2 may be used to redirect the light toward Beam Combiner (BC), which may serve to reflect the output of one light source, while transmitting the other. The output of LS1 and LS2 may be of different color, or wavelength, or spectral band, or they may be the same. If they are different, BC may be a dichroic mirror,

or other such spectrally discriminating optical element. If the outputs of Light Sources LS1 and LS2 are spectrally similar, BC may utilize polarization to combine the beams. Lens L3 may be used to couple the W1 and W2 into Waveguide (WG). Lenses L1 and L2 may also be replaced by other optical elements, such as mirrors, etc. This method is extensible to greater numbers of light sources.

The type of optical fiber that may be used as either delivery segments or within the applicators is varied, and may be selected from the group consisting of: Step-index, GRIN ("gradient index"), Power-Law index, etc. Alternately, hollow-core waveguides, photonic crystal fiber (PCF), and/or fluid filled channels may also be used as optical conduits. PCF is meant to encompass any waveguide with the ability to confine light in hollow cores or with confinement characteristics not possible in conventional optical fiber. More specific categories of PCF include photonic-bandgap fiber (PBG, PCFs that confine light by band gap effects), holey fiber (PCFs using air holes in their cross-sections), hole-assisted fiber (PCFs guiding light by a conventional higher-index core modified by the presence of air holes), and Bragg fiber (PBG formed by concentric rings of multilayer film). These are also known as "microstructured fibers". End-caps or other enclosure means may be used with open, hollow waveguides such as tubes and PCF to prevent fluid infill that would spoil the waveguide.

PCF and PBG intrinsically support higher numerical aperture (NA) than standard glass fibers, as do plastic and plastic-clad glass fibers. These provide for the delivery of lower brightness sources, such as LEDs, OLEDs, etc. This is notable for certain embodiments because such lower brightness sources are typically more electrically efficient than laser light

sources, which is relevant for implantable device embodiments in accordance with the present invention that utilize battery power sources. Configurations for creating high-NA waveguide channels are described in greater detail herein.

Alternately, a bundle of small and/or single mode (SM) optical fibers/waveguides may be used to transport light as delivery segments, and/or as an applicator structure, such as is shown in a non-limiting exemplary embodiment in Figure 16A. In this embodiment, Waveguide (WG) may be part of the Delivery Segment(s) (DS), or part of the applicator (A) itself. As shown in the embodiment of Figure 16A, the waveguide (WG) bifurcates into a plurality of subsequent waveguides, BWGx. The terminus of each BWGx is Treatment Location (TLx). The terminus may be the area of application/target illumination, or may alternately be affixed to an applicator for target illumination. Such a configuration is appropriate for implantation within a distributed body tissue, such as, by way of non-limiting example, the liver, pancreas, or to access cavernous arteries of the corpora cavernosa.

Referring to Figure 16B, the waveguide (WG) may also be configured to include Undulations (U) in order to accommodate possible motion and/or stretching/constricting of the target tissues, or the tissues surrounding the target tissues, and minimize the mechanical load (or "strain") transmitted to the applicator from the delivery segment and vice versa. Undulations (U) may be pulsed straight during tissue extension and/or stretching. Alternately, Undulations (U) may be integral to the applicators itself, or it may be a part of the Delivery Segments (DS) supplying the applicator (A). The Undulations (U) may be made to areas of output coupling in embodiments when the Undulations (U) are in the applicator. This may be achieved by

means of similar processes to those described earlier regarding means by which to adjust the refractive index and/or the mechanical configuration(s) of the waveguide for fixed output coupling in an applicator. However, in this case, the output coupling is achieved by means of tissue movement that causes such changes. Thus, output coupling is nominally only provided during conditions of tissue extension and/or contraction and/or motion. The Undulations (U) may be configured of a succession of waves, or bends in the waveguide, or be coils, or other such shapes. Alternately, DS containing Undulations (U) may be enclosed in a protective sheath or jacket to allow DS to stretch and contract without encountering tissue directly.

A rectangular slab waveguide may be configured to be like that of the aforementioned helical-type, or it can have a permanent waveguide (WG) attached/inlaid. For example, a slab may be formed such that is a limiting case of a helical-type applicator, such as is illustrated in Figure 17 for explanatory purposes and to make the statement that the attributes and certain details of the aforementioned helical-type applicators are suitable for this slab-like as well and need not be repeated.

In the embodiment depicted in Figure 17, Applicator (A) is fed by Delivery Segment (DS) and the effectively half-pitch helix is closed along the depicted edge (E), with closure holes (CH) provided, but not required. Of course, this is a reduction of the geometries discussed previously, and meant to convey the abstraction and interchangeability of the basic concepts therein and between those of the slab-type waveguides to be discussed.

It should also be understood that the helical-type applicator described herein may also be utilized as a straight applicator, such as may be used to provide illumination along a

linear structure like a nerve, etc. A straight applicator may also be configured as the helical-type applicators described herein, such as with a reflector to redirect stray light toward the target, as is illustrated in Figure 18A by way of non-limiting example.

Here Waveguide (WG) contains Textured Area (TA), and the addition of Reflector (M) that at least partially surrounds target anatomy (N). This configuration provides for exposure of the far side of the target by redirecting purposefully exposed and scattered light toward the side of the target opposite the applicator. Figure 18B illustrates the same embodiment, along cross-section A-A in Figure 18A, showing schematically the use of a mirror (as Reflector M) surrounding Target (N.) Although not shown, WG and M may be affixed to a common casing (not shown) that forms part of the applicator. Reflector (M) is shown as being comprised of a plurality of linear faces, but need not be. In one embodiment it may be made to be a smooth curve, or in another embodiment, a combination of the two.

In another alternate embodiment, a straight illuminator may be affixed to the target, or tissue surrounding or adjacent or nearby to the target by means of the same helix-type ("helical") applicator. However, in this case the helical portion is not the illuminator, it is the means to position and maintain another illuminator in place with respect to the target. The embodiment illustrated in Figure 19 utilizes the target-engaging feature(s) of the helical-type applicator to locate straight-type Applicator (A) in position near Target (N) via Connector Elements CE1 and CE2, which engage the Support Structure (D) to locate and maintain optical output. Output illumination is shown as being emitted via Textured Area (TA), although, as already discussed, alternate output coupling means are also

within the scope of the present invention. The generality of the approach and the interchangeability of the different target-engaging means described herein (even subsequent to this section) are also applicable to serve as such Support Structures (D), and therefore the combination of them is also within the scope of the present invention.

Slab-type ("slab-like") geometries of Applicator A, such as thin, planar structures, can be implanted, or installed at, near, or around the tissue target or tissue(s) containing the intended target(s). An embodiment of such a slab-type applicator configuration is illustrated in Figures 20A-20C. It may be deployed near or adjacent to a target tissue, and it may also be rolled around the target tissue, or tissues surrounding the target(s). It may be rolled axially, as illustrated by element AM1 in Figure 20B, (i.e. concentric with the long axis of the targeted tissue structure N), or longitudinally, as illustrated by element AM2 in Figure 20C (i.e. along the long axis of target N), as required by the immediate surgical situation. The lateral edges that come into contact with each other once deployed at the target location could be made with complementary features to assure complete coverage and limit the amount of cellular infiltrate (i.e. limit scar tissue or other optical perturbations over time to better assure an invariant target irradiance, as was described in the earlier section pertaining to the helical-type applicator). Closure Holes (CH) are provided for this purpose in the figure of this non-limiting example. The closure holes (CH) may be sutured together, of otherwise coupled using a clamping mechanism (not shown). It may also provide different output coupling mechanisms than the specific helical-type waveguides described above, although, it is to be understood that such mechanisms are fungible, and may

be used generically. And vice versa, that elements of output coupling, optical recirculation and waveguiding structures, as well as deployment techniques discussed in the slab-type section may be applicable to helical-type, and straight waveguides.

The slab-type applicator (A) illustrated in Figures 20A-20C is comprised of various components, as follows. In the order "seen" by light entering the applicator, first is an interface with the waveguide of the delivery segment (DS). Alternately, the waveguide may be replaced by electrical wires, in the case where the emitter(s) is(are) included near or within the applicator. An Optical Plenum (OP) structure may be present after the interface to segment and direct light propagation to different channels CH using distribution facets (DF), whether it comes from the delivery segments (DS), or from a local light source. The optical plenum (OP) may also be configured to redirect all of the light entering the light entering it, such as might be desirable when the delivery segment (DS) should lie predominantly along the same direction as the applicator (A). Alternately, it may be made to predominantly redirect the light at angle to provide for the applicator to be directed differently than the delivery segment(s) (DS). Light propagating along the channel(s) (CH) may encounter an output coupling means, such as Partial Output Coupler (POC) and Total Output Coupler (TOC). The proximal output couplers (POC) redirect only part of the channeled light, letting enough light pass to provide adequate illumination to more distal targets, as was discussed previously. The final, or distal-most, output coupler (TOC) may be made to redirect nominally all of the impinging light to the target. The present embodiment also contains provisions for outer surface reflectors to redirect errant light to the target. It is also configured to support a

reflector (RE) on or near the inner surface (IS) of applicator (A), with apertures (AP) to allow for the output coupled light to escape, that serves to more readily redirect any errant or scattered light back toward the target (N). Alternately, such a reflector (RE) may be constructed such that it is not covering the output coupler area, but proximal to it in the case of longitudinally rolled deployment such that it nominally covers the intended target engagement area (TEA). Reflector (RE) may be made from biocompatible materials such as platinum, or gold if they are disposed along the outside of the applicator (A). Alternately, such metallic coatings may be functionalized in order to make them bioinert, as is discussed below. The output couplers POC and TOC are shown in Figure 20A as being located in the area of the applicator (A) suitable for longitudinal curling about the target (N) (Figure 20B), or tissues surrounding the target (N), but need not be, as would be the case for deployments utilizing the unrolled and axially rolled embodiments (AM1). Any such surface (or sub-surface) reflector (RE) should be present along (or throughout) a length sufficient to provide at least complete circumferential coverage once the applicator is deployed. As used herein the terms optical conduit and channel member are equivalent.

The current embodiment utilizes PDMS, described below, or some other such well-qualified polymer, as a substrate (SUB) that forms the body of the applicator (A), for example as in Figure 20A. For example, biological materials such as hyaluronan, elastin, and collagen, which are components of the native extracellular matrix, may also be used alone or in combination with inorganic compounds to form the substrate (SUB). Hydrogel may also be used, as it is biocompatible, may be made to elute biological and/or pharmaceutical compounds, and

has a low elastic modulus, making it a compliant material. Likewise polyethylene, and/or polypropylene may also be used to fro Substrate SUB.

A material with a refractive index lower than that of the substrate (SUB) (PDMS in this non-limiting example) may be used as filling (LFA) to create waveguide cladding where the PDMS itself acts as the waveguide core. In the visible spectrum, the refractive index of PDMS is ~1.4. Water, and even PBS and saline have indices of ~1.33, making them suitable for cladding materials. They are also biocompatible and safe for use in an illumination management system as presented herein, even if the integrity of the applicator (A) is compromised and they are released into the body.

Alternately, a higher index filling may be used as the waveguide channel. This may be thought of as the inverse of the previously described geometry, where in lieu of the polymer comprising substrate (SUB), you have a liquid filling (LFA) acting as the waveguide core medium, and the substrate (SUB) material acting as the cladding. Many oils have refractive indices of ~1.5 or higher, making them suitable for core materials.

Alternately, a second polymer of differing refractive index may be used instead of the aforementioned liquid fillings. A high-refractive-index polymer (HRIP) is a polymer that has a refractive index greater than 1.50. The refractive index is related to the molar refractivity, structure and weight of the monomer. In general, high molar refractivity and low molar volumes increase the refractive index of the polymer. Sulfur-containing substituents including linear thioether and sulfone, cyclic thiophene, thiadiazole and thianthrene are the most commonly used groups for increasing refractive index of a

polymer in forming a HRIP. Polymers with sulfur-rich thianthrene and tetrathiaanthrene moieties exhibit n values above 1.72, depending on the degree of molecular packing. Such materials may be suitable for use as waveguide channels within a lower refractive polymeric substrate. Phosphorus-containing groups, such as phosphonates and phosphazenes, often exhibit high molar refractivity and optical transmittance in the visible light region. Polyphosphonates have high refractive indices due to the phosphorus moiety even if they have chemical structures analogous to polycarbonates. In addition, polyphosphonates exhibit good thermal stability and optical transparency; they are also suitable for casting into plastic lenses. Organometallic components also result in HRIPs with good film forming ability and relatively low optical dispersion. Polyferrocenylsilanes and polyferrocenes containing phosphorus spacers and phenyl side chains show unusually high n values (n=1.74 and n=1.72), as well, and are also candidates for waveguides.

Hybrid techniques which combine an organic polymer matrix with highly refractive inorganic nanoparticles may be employed to produce polymers with high n values. As such, PDMS may also be used to fabricate the waveguide channels that may be integrated to a PDMS substrate, where native PDMS is used as the waveguide cladding. The factors affecting the refractive index of a HRIP nanocomposite include the characteristics of the polymer matrix, nanoparticles, and the hybrid technology between inorganic and organic components. Linking inorganic and organic phases is also achieved using covalent bonds. One such example of hybrid technology is the use of special bifunctional molecules, such as 3-Methacryloxypropyltrimethoxysilane (MEMO), which possess a polymerisable group as well as alkoxy groups.

Such compounds are commercially available and can be used to obtain homogeneous hybrid materials with covalent links, either by simultaneous or subsequent polymerization reactions.

The following relation estimates the refractive index of a nanocomposite,

$$n_{comp} = \phi_p n_p + \phi_{org} n_{org}$$

where, n_{comp}, n_p and n_{org} stand for the refractive indices of the nanocomposite, nanoparticle and organic matrix, respectively, while ϕ_p and ϕ_{org} represent the volume fractions of the nanoparticles and organic matrix, respectively.

The nanoparticle load is also important in designing HRIP nanocomposites for optical applications, because excessive concentrations increase the optical loss and decrease the processability of the nanocomposites. The choice of nanoparticles is often influenced by their size and surface characteristics. In order to increase optical transparency and reduce Rayleigh scattering of the nanocomposite, the diameter of the nanoparticle should be below 25 nm. Direct mixing of nanoparticles with the polymer matrix often results in the undesirable aggregation of nanoparticles - this may be avoided by modifying their surface, or thinning the viscosity of the liquid polymer with a solvent such as xylene; which may later be removed by vacuum during ultrasonic mixing of the composite prior to curing. Nanoparticles for HRIPs may be chosen from the group consisting of: TiO_2 (anatase, n=2.45; rutile, n=2.70), ZrO_2 (n=2.10), amorphous silicon (n=4.23), PbS (n=4.20) and ZnS (n=2.36). Further materials are given in the table below. The

resulting nanocomposites may exhibit a tunable refractive index range, per the above relation.

Substance	n (@1.3 mm)	n (@0.589 mm)
Si	4.05	3.96
W	3.35	3.40
Si crystalline	5.22	3.91
Si amorphous	4.38	4.23
Ge	4.08	5.59–5.64
GaP	4.08	3.31
GaAs	4.51	3.87
InP	4.40	3.55
InAs	3.30	4.00
InSb	3.37	4.19
PbS	3.88	4.29
PbSe	1.25–3.80	3.85–3.90
PbTe	1.0–1.8	6.40
Ag	0.17	0.13
Au	1.64	0.19
Cu	1.18	0.27

In one exemplary embodiment, a HRIP preparation based on PDMS and PbS, the volume fraction of particles needs to be around 0.2 or higher to yield $n_{comp} \geq 1.96$, which corresponds to a weight fraction of at least 0.8 (using the density of PbS of 7.50 g cm^{-3} and of PDMS of 1.35 g cm^{-3}). Such a HRIP can support a high numerical aperture (NA), which is useful when coupling light from relatively low brightness sources such as LEDs. The information given above allows for the recipe of other alternate formulations to be readily ascertained.

There are many synthesis strategies for nanocomposites. Most of them can be grouped into three different types. The preparation methods are all based on liquid particle dispersions, but differ in the type of the continuous phase. In melt processing particles are dispersed into a polymer melt and nanocomposites are obtained by extrusion. Casting methods use a polymer solution as dispersant and solvent evaporation yields the composite materials, as described earlier. Particle

dispersions in monomers and subsequent polymerization result in nanocomposites in the so-called in situ polymerization route.

In a similar way, low refractive index composite materials may also be prepared. As suitable filler materials, metals with low refractive indices below 1, such as gold (shown in the table above) may be chosen, and the resulting low index material used as the waveguide cladding.

There are a variety of optical plenum configurations for capturing light input and creating multiple output channels. As shown in Figures 20A-20C and 22 the facets are comprised of linear faces, although other configurations are within the scope of the invention. The angle of the face with respect to the input direction of the light dictates the numerical aperture (NA). Alternately, curved faces may be employed for nonlinear angular distribution and intensity homogenization. A parabolic surface profile may be used, for example. Furthermore, the faces need not be planar. A three-dimensional surface may similarly be employed. The position of these plenum distribution facets DF may be used to dictate the proportion of power captured as input to a channel, as well. Alternately, the plenum distribution facets DF may spatially located in accordance with the intensity/irradiance distribution of the input light source. As a non-limiting example, in a configuration utilizing an input with a Lambertian irradiance distribution, such as that which may be output by an LED, the geometry of the distribution facets DF may be tailored to limit the middle channel to have 1/3 of the emitted light, and the outer channels evenly divide the remaining 2/3, such as is shown in Figure 21 by way of non-limiting example.

Output Coupling may be achieved many ways, as discussed earlier. Furthering that discussion, and to be considered as

part thereof, scattering surfaces in areas of intended emission may be utilized. Furthermore, output coupling facets, such as POC and TOC shown previously, may also be employed. These may include reflective, refractive, and/or scattering configurations. The height of facet may be configured to be in proportion to the amount or proportion of light intercepted, while the longitudinal position dictates the output location. As was also discussed previously, for systems employing multiple serial OCs, the degree of output coupling of each may be made to be proportional to homogenize the ensemble illumination. A single-sided facet within the waveguide channel may be disposed such that it predominantly captures light traveling one way down the waveguide channel (or core). Alternately, a double-sided facet that captures light traveling both ways down the waveguide channel (or core) to provide both forward and backward output coupling. This would be used predominantly with distal retroreflector designs. Such facets may be shaped as, by way of non-limiting example; a pyramid, a ramp, an upward-curved surface, a downward-curved surface, etc. Figure 22 illustrates output coupling for a ramp-shaped facet.

Light Ray ER enters (or is propagated within) Waveguide Core WG. It impinges upon Output Coupling Facet F and is redirected to the opposite surface. It becomes Reflected Ray RR1, from which Output Coupled Ray OCR1 is created, as is Reflected Ray RR2. OCR1 is directed at the target. OCR2 and RR3 are likewise created from RR2. Note that OCR2 is emitted from the same surface of WG as the facet. If there is no target or reflector on that side, the light is lost. The depth of F is H, and the Angle θ. Angle θ dictates the direction of RR1, and its subsequent rays. Angle α may be provided in order to allow

for mold release for simplified fabrication. It may also be used to output couple light traversing in the opposite direction as ER, such as might be the case when distal retro-reflectors are used.

Alternately, Output Coupling Facet F may protrude from the waveguide, allowing for the light to be redirected in an alternate direction, but by similar means.

The descriptions herein regarding optical elements, such as, but limited to, Applicators and Delivery Segments may also be utilized by more than a single light source, or color of light, such as may be the case when using SFO, and/or SSFO opsins, as described in more detail elsewhere herein.

The waveguide channel(s) may be as described above. Use of fluidics may also be employed to expand (or contract) the applicator to alter the mechanical fit, as was described above regarding Sleeve S. When used with an applicator (A) such as that depicted in Figures 20A-C it may serve to decrease infiltrate permeability as well as to increase optical penetration via pressure-induced tissue clearing. Tissue clearing, or optical clearing as it is also known, refers to the reversible reduction of the optical scattering by a tissue due to refractive index matching of scatterers and ground matter. This may be accomplished by impregnating tissue with substances ("clearing agents") such as, x-ray contrast agents (e.g. Verografin, Trazograph, and Hypaque-60), glucose, propylene glycol, polypropylene glycol-based polymers (PPG), polyethylene glycol (PEG), PEG-based polymers, and glycerol by way of non-limiting examples. It may also be accomplished by mechanically compressing the tissue.

Fluidic channels incorporated into the applicator substrate may also be used to tune the output coupling facets. Small

reservoirs beneath the facets may be made to swell and in turn distend the location and/or the angle of the facet in order to adjust the amount of light and/or the direction of that light.

Captured light may also be used to assess efficiency or functional integrity of the applicator and/or system by providing information regarding the optical transport efficiency of the device/tissue states. The detection of increased light scattering may be indicative of changes in the optical quality or character of the tissue and or the device. Such changes may be evidenced by the alteration of the amount of detected light collected by the sensor. It may take the form of an increase or a decrease in the signal strength, depending upon the relative positions of the sensor and emitter(s). An opposing optical sensor may be employed to more directly sample the output, as is illustrated in Figure 23. In this non-limiting embodiment, Light Field LF is intended to illuminate the Target (N) via output coupling from a waveguide within Applicator A, and stray light is collected by Sensor SEN1. SEN1 may be electrically connected to the Housing (not shown) via Wires SW1 to supply the Controller with information regarding the intensity of the detected light. A second Sensor SEN2 is also depicted. Sensor SEN2 may be used to sample light within a (or multiple) waveguides of Applicator A, and its information conveyed to a controller (or processor) via Wires SW2. This provides additional information regarding the amount of light propagating within the Waveguide(s) of the Applicator. This additional information may be used to better estimate the optical quality of the target exposure by means of providing a baseline indicative of the amount of light energy or power that is being emitted via the resident output coupler(s), as being proportional to the conducted light within the Waveguide(s).

Alternately, the temporal character of the detected signals may be used for diagnostic purposes. For example, slower changes may indicate tissue changes or device aging, while faster changes could be strain, or temperature dependent fluctuations. Furthermore, this signal may be used for closed loop control by adjusting power output over time to assure more constant exposure at the target. The detected signal of a Sensor such as SEN1 may also be used to ascertain the amount of optogenetic protein matter present in the target. If such detection is difficult to the proportionately small effects on the signal, a heterodyned detection scheme may be employed for this purpose. Such an exposure may be of insufficient duration or intensity to cause a therapeutic effect, but made solely for the purposes of overall system diagnostics.

Alternately, an applicator may be fabricated with individually addressable optical source elements to enable adjustment of the intensity and location of the light delivery, as is shown in the embodiment of Figure 24 (1010). Such applicators may be configured to deliver light of a single wavelength to activate or inhibit nerves. Alternately, they may be configured to deliver light of two or more different wavelengths, or output spectra, to provide for both activation and inhibition in a single device, or a plurality of devices.

An alternate example of such an applicator is shown in Figure 25, where Applicator A is comprised of Optical Source Elements LSx, may be comprised of Emitters (EM), mounted on Bases B; element "DS"xx represents the pertinent delivery segments as per their coordinates in rows/columns on the applicator (A); element "SUB" represents the substrate, element "CH" represents closure holes, and element "TA" a textured area, as described above.

The optical sensors described herein are also known as photodetectors, and come in different forms. These may include, by way of non-limiting examples, photovoltaic cells, photodiodes, pyroelectrics, photoresistors, photoconductors, phototranisistors, and photogalvanic devices. A photogalvanic sensor (also known as a photoelectrochemical sensor) may be constructed by allowing a conductor, such as stainless steel or platinum wire, to be exposed on, at, or adjacent to a target tissue. Light being remitted from the target tissue that impinges upon the conductor will cause it undergo a photogalvanic reaction that produces a electromotive force, or "EMF", with respect to another conductor, or conductive element, that is at least substantially in the same electrical circuit as the sensor conductor, such as it may be if immersed in the same electrolytic solution (such as is found within the body). The EMF constitutes the detector response signal. That signal may then be used as input to a system controller in order to adjust the output of the light source to accommodate the change. For example, the output of the light source may be increased, if the sensor signal decreases and vice versa.

In an alternate embodiment, an additional sensor, SEN2, may also be employed to register signals other than those of sensor SEN1 for the purposes of further diagnosing possible causes of systemic changes.

For example, the target opacity and/or absorbance may be increasing if SEN2 maintains a constant level indicating that the optical power entering the applicator is constant, but sensor SEN1 shows a decreasing level. A commensurate decrease in the response of sensor SEN2 would indicate that the electrical power to the light source should be increased to accommodate a decline in output and/or efficiency, as might be

experienced in an aging device. Thus, an increase in optical power and/or pulse repetition rate delivered to the applicator may mitigate the risk of underexposure to maintain a therapeutic level.

Changes to the optical output of the light source may be made to, for example, the output power, exposure duration, exposure interval, duty cycle, pulsing scheme, pulse duration, pulse interval, irradiance, and/or duty cycle.

For the exemplary configuration shown in Figure 23, the following table may be used to describe exemplary programming for the controller in each case of sensor response changes.

SEN1 Response Change	SEN2 Response Change	Possible Cause(s)	Possible Action(s)
Decrease	Decrease	Light source output or overall optical system efficiency diminishing.	Increase electrical input power to light source to increase optical output power and regain expected signal from SEN1 and/or

			SEN2, and/or monitor therapeutic outcome. Otherwise, replacement of the light source is possibly indicated.
Decrease	Constant	Change in target optical characteristics, such as tissue or cellular ingrowth between the applicator and target tissue, or relative movement between applicator and target.	Increase electrical input power to light source to increase optical output power and regain expected signal from SEN1 while resetting baseline for

			SEN2 signal level, and/or monitor therapeutic outcome. Otherwise, replacement of the applicator is possibly indicated.
Decrease	Increase	The amount of light diverted to SEN2 increasing.	Increase electrical input power to light source to increase optical output power and regain expected signal from SEN1 while resetting baseline for SEN2 signal

			level, and/or monitor therapeutic outcome. Otherwise, replacement of the applicator is possibly indicated.
Constant	Decrease	Change in target optical characteristics, such as tissue or cellular ingrowth between the applicator and target tissue.	Maintain light source output level while resetting baseline for SEN2 signal level, and/or monitor therapeutic outcome.
Constant	Increase	Change in the optical delivery efficiency of the applicator.	Maintain light source output level while resetting

			baseline for SEN2 signal level.
Increase	Decrease	Change in target optical characteristics, or movement of applicator with respect to target tissue.	Maintain light source output level while resetting baseline for SEN1 and SEN2 signal levels, and/or monitor therapeutic outcome.
Increase	Constant	Change in target optical characteristics, or movement of applicator with respect to target tissue.	Maintain light source output level while resetting baseline for SEN1 signal level, and/or monitor therapeutic outcome.

			Decrease electrical input power to light source to increase optical output power and regain expected signal from SEN1 while resetting baseline for SEN2 signal level, if original setting is not achieved, and/or monitor therapeutic outcome. Otherwise, replacement of the applicator
Increase	Increase	Change in the optical output and/or delivery efficiency of the system.	

			is possibly indicated.

It is to be understood that the term "constant" does not simply imply that there is no change in the signal or its level, but maintaining its level within an allowed tolerance. Such a tolerance may be of the order of ±20% on average. However, patient and other idiosyncrasies may also be need to be accounted and the tolerance band adjusted on a per patient basis where a primary and/or secondary therapeutic outcome and/or effect is monitored to ascertain acceptable tolerance band limits. As is shown in Figure 5, an overexposure is not expected to cause diminished efficacy. However, the desire to conserve energy while still assuring therapeutic efficacy compels that overexposures be avoided to increase both battery lifetime and the recharge interval for improved patient safety and comfort.

Alternately, SEN2 may be what we will refer to as a therapeutic sensor configured to monitor a physical therapeutic outcome directly, or indirectly. Such a therapeutic sensor may be, by way of non-limiting example, an electrical sensor, an electrode, an ENG probe, an EMG probe, a pressure transducer, a chemical sensor, an EKG sensor, or a motion sensor. A direct sensor is considered to be one that monitors a therapeutic outcome directly, such as the aforementioned examples of chemical and pressure sensors. An indirect sensor is one that monitors an effect of the treatment, but not the ultimate result. Such sensors are the aforementioned examples of ENG, EKG, and EMG probes, as are also discussed elsewhere herein.

Alternately, the therapeutic sensor may be a patient input device that allows the patient to at least somewhat dictate the optical dosage and/or timing. Such a configuration may be utilized, by way of non-limiting example, in cases such as muscle spasticity, where the patient may control the optical dosage and/or timing to provide what they deem to be the requisite level of control for a given situation.

In an alternate embodiment, an additional optical sensor may be located at the input end of the delivery segment near to the light source. This additional information may assist in diagnosing system status by allowing for the optical efficiency of the delivery segments to be evaluated. For example, the delivery segments and/or their connection to the applicator may be considered to be failing, if the output end sensor registers a decreasing amount of light, while the input end sensor does not. Thus, replacing the delivery segments and/or the applicator may be indicated.

In an alternate embodiment, SEN1 may further be configured to utilize a collector, such as an optical fiber, or at least an aspect of the Applicator itself, that serves to collect and carry the optical signal from, or adjacent to the Applicator to a remote location. By way of non-limiting example, light may be sampled at or near the target tissue, but transferred to the controller for detection and processing. Such a configuration is shown in Figure 55, where Delivery Segment DS provides light to Applicator A, creating Light Field LF. Light Field LF is sampled by Collection Element COL-ELEM, which may be, by way of non-limiting example, a prism, a rod, a fiber, a side-firing fiber, a cavity, a slab, a mirror, a diffractive element, and/or a facet. Collected Light COL-LIGHT is transmitted by Waveguide WG2 to SEN1, not shown.

Alternately, the Delivery Segment itself, or a portion thereof, may be used to transmit light to the remote location of SEN1 by means of spectrally separating the light in the housing. This configuration may be similar to that shown in Figure 15, with the alterations, that LS2 becomes SEN1, and Beamcombiner BC is configured such that it allows light from the target tissue to be transmitted to SEN1, while still allowing substantially all of the light form LS1 to be injected into Waveguide WG for therapeutic and diagnostic purposes. Such a configuration may be deployed when SEN1 may be a chemometric sensor, for example, and a fluorescence signal may be the desired measurand.

The system may be tested at the time of implantation, or subsequent to it. The tests may provide for system configurations, such as which areas of the applicator are most effective, or efficacious, by triggering different light sources alone, or in combination, to ascertain their effect on the patient. This may be utilized when a multi-element system, such as an array of LEDs, for example, or a multiple output coupling method is used. Such diagnostic measurements may be achieved by using an implanted electrode that resides on, in or near the applicator, or one that was implanted elsewhere, as will be described in another section. Alternately, such measurements may be made at the time of implantation using a local nerve electrode for induced stimulation, and/or an electrical probe to query the nerve impulses intraoperatively using a device such as the Stimulator/Locator sold under the tradename CHECKPOINT® from NDI and Checkpoint Surgical, Inc. to provide electrical stimulation of exposed motor nerves or muscle tissue and in turn locate and identify nerves as well to test their excitability. Once obtained, an applicator illumination configuration may be programmed into the system for optimal therapeutic outcome using

an external Programmer/Controller (P/C) via a Telemetry Module (TM) into the Controller, or Processor / CPU of the system Housing (H), as are defined further below.

The electrical connections for devices such as these where the light source is either embedded within, on, or located nearby to the applicator, may be integrated into the applicators described herein. Materials like the product sold by NanoSonics, Inc. under the tradename Metal Rubber™ and/or mc10's extensible inorganic flexible circuit platform may be used to fabricate an electrical circuit on or within an applicator. Alternately, the product sold by DuPont, Inc., under the tradename PYRALUX®, or other such flexible and electrically insulating material, like polyimide, may be used to form a flexible circuit; including one with a copper-clad laminate for connections. PYRALUX® in sheet form allows for such a circuit to be rolled. More flexibility may be afforded by cutting the circuit material into a shape that contains only the electrodes and a small surrounding area of polyimide.

Such circuits then may be encapsulated for electrical isolation using a conformal coating. A variety of such conformal insulation coatings are available, including by way of non-limiting example, parlene (Poly-Para-Xylylene) and parlene-C (parylene with the addition of one chlorine group per repeat unit), both of which are chemically and biologically inert. Silicones and polyurethanes may also be used, and may be made to comprise the applicator body, or substrate, itself. The coating material can be applied by various methods, including brushing, spraying and dipping. Parylene-C is a bio-accepted coating for stents, defibrillators, pacemakers and other devices permanently implanted into the body.

In a particular embodiment, biocompatible and bio-inert coatings may be used to reduce foreign body responses, such as that may result in cell growth over or around an applicator and change the optical properties of the system. These coatings may also be made to adhere to the electrodes and to the interface between the array and the hermetic packaging that forms the applicator.

By way of non-limiting example, both parylene-C and poly(ethylene glycol) (PEG, described herein) have been shown to be biocompatible and may be used as encapsulating materials for an applicator. Bioinert materials non-specifically downregulate, or otherwise ameliorate, biological responses. An example of such a bioinert material for use in an embodiment of the present invention is phosphoryl choline, the hydrophilic head group of phospholipids (lecithin and sphingomyelin), which predominate in the outer envelope of mammalian cell membranes. Another such example is Polyethylene oxide polymers (PEO), which provide some of the properties of natural mucous membrane surfaces. PEO polymers are highly hydrophilic, mobile, long chain molecules, which may trap a large hydration shell. They may enhance resistance to protein and cell spoliation, and may be applied onto a variety of material surfaces, such as PDMS, or other such polymers. An alternate embodiment of a biocompatible and bioinert material combination for use in practicing the present invention is phosphoryl choline (PC) copolymer, which may be coated on a PDMS substrate. Alternately, a metallic coating, such as gold or platinum, as were described earlier, may also be used. Such metallic coatings may be further configured to provide for a bioinert outer layer formed of self-assembled monolayers (SAMs) of, for example, D-mannitol-terminated alkanethiols. Such a SAM may be produced by soaking

the intended device to be coated in 2 mM alkanethiol solution (in ethanol) overnight at room temperature to allow the SAMs to form upon it. The device may then be taken out and washed with absolute ethanol and dried with nitrogen to clean it.

A variety of embodiments of light applicators are disclosed herein. There are further bifurcations that depend upon where the light is produced (i.e., in or near the applicator vs. in the housing or elsewhere). Figures 26A and 26B illustrate these two configurations.

Referring to Figure 26A, in a first configuration, light is generated in the housing and transported to the applicator via the delivery segment. The delivery segment(s) may be optical waveguides, selected from the group consisting of round fibers, hollow waveguides, holey fibers, photonic bandgap devices, and/or slab configurations, as have described previously. Multiple waveguides may also be employed for different purposes. As a non-limiting example, a traditional circular cross-section optical fiber may be used to transport light from the source to the applicator because such fibers are ubiquitous and may be made to be robust and flexible. Alternately, such a fiber may be used as input to another waveguide, this with a polygonal cross-section providing for regular tiling. Such waveguides have cross-sectional shapes that pack together fully, i.e. they form an edge-to-edge tiling, or tessellation, by means of regular congruent polygons. That is, they have the property that their cross-sectional geometry allows them to completely fill (pack) a two-dimensional space. This geometry yields the optical property that the illumination may be made to spatially homogeneous across the face of such a waveguide. Complete homogeneity is not possible with other geometries, although they may be made to have fairly homogeneous irradiation profiles

nonetheless. For the present application, a homogenous irradiation distribution may be utilized because it may provide for uniform illumination of the target tissue. Thus, such regular-tiling cross-section waveguides may be useful. It is also to be understood that this is a schematic representation and that multiple applicators and their respective delivery segments may be employed. Alternately, a single delivery segment may service multiple applicators. Similarly, a plurality of applicator types may also be employed, based upon the clinical need.

Referring to the configuration of Figure 26B, light is generated in the applicator. The power to generate the optical output is contained within the housing and is transported to the applicator via the delivery segment. It is to be understood that this is a schematic representation and that multiple applicators and their respective delivery segments may be employed. Similarly, a plurality of applicator types may also be employed.

The size(s) of these applicators may be dictated by the anatomy of the target tissue. By way of non-limiting example, a fluidic channel slab-type (or, equivalently, "slab-like") applicator may be configured to comprise a parallel array of 3 rectangular HRIP waveguides that are 200μm on a side, the applicator may be between 1-10mm in width and between 5-100mm in length, and provide for multiple output couplers along the length of each channel waveguide to provide a distributed illumination of the target tissue.

The pertinent delivery segments may be optical waveguides, such as optical fibers, in the case where the light is not generated in or near the applicator(s). Alternately, when the light is generated at or near the applicator(s), the delivery

segments may be electrical wires. They may be further comprised of fluidic conduits to provide for fluidic control and/or adjustment of the applicator(s). They may also be any combination thereof, as dictated by the specific embodiment utilized, as have been previously described.

Embodiments of the subject system may be partially, or entirely, implanted in the body of a patient. Figure 27 illustrates this, wherein the left hand side of the illustration schematically depicts the partially implanted system, and the right hand side of the illustration the fully implanted device. The housing H may be implanted, carried, or worn on the body (B), along with the use of percutaneous feedthroughs or ports for optical and/or electrical conduits that comprise the delivery segments (various embodiments/denotations of DS, or "DSx", as per the Figures) that connect to Applicator(s) A implanted to irradiate target tissue(s) N. In this exemplary embodiment, a Transcutaneous Optical Feedthrough COFT may be coupled to the Delivery Segments affixed to Housing H, located in Extracorporeal Space ES, while Applicator A is in the Intracorporeal Space IS along with Target Tissue N.

Figure 56 shows an embodiment of a transcutaneous optical feedthrough, or port, comprising, by way of non-limiting example, an External Delivery Segment DSE, which in turn is routed through a seal, comprised of, External Sealing Element SSE that resides in the extracorporeal space ES, and Internal Sealing Element SSI that resides in the intracorporeal space IS. These sealing elements may held together by means of Compression Element COMPR to substantially maintain an infection-free seal for Transcutaneous Optical Feedthrough COFT. Internal Seal SSI, may comprise a medical fabric sealing surface along with a more rigid member coupled thereto to more substantially impart the

compressive force from Compression Element COMPR when forming a percutaneous seal. The medical fabric/textile may be selected from the list consisting of, by way of non-limiting examples; dacron, polyethylene, polypropylene, silicone, nylon, and PTFE. Woven and/or non-woven textiles may be used as a component of Internal Seal SSI. The fabric, or a component thereon, may also be made to elute compounds to modulate wound healing and improve the character of the seal. Such compounds, by way of non-limiting examples, may be selected from the list consisting of; Vascular Endothelial Growth Factor (VEGF), glycosaminoglycans (Gags), and other cytokines. Applicable medical textiles may be available from vendors, such as Dupont and ATEX Technologies, for example. Delivery Segment DS may be connected to the optical and/or electrical connections of Applicator A, not shown for purposes of clarity, not shown. External Delivery Segment DSE may be may be connected to the optical and/or electrical output of Housing H, not shown for purposes of clarity. The surface of the patient, indicated in this example as Skin SKIN, may offer a natural element by way of the epidermis onto which the seal may be formed. Details regarding the means of sealing External Delivery Segment DES, which passes through the Skin SKIN, to Compression Element COMPR are discussed elsewhere herein in regards to optical feedthroughs within Housing H, such as are shown in Figures 57A-59.

Figures 57A and 57B show an alternate embodiment of an implantable, hermetically sealed Housing H comprising an optical feed-through OFT, wherein Delivery Segment DSx may be coupled to Housing H. The system further may comprise a configuration such that Delivery Segment DSx may be coupled to Housing H via a plurality of electrical connections and at least one optical connection via Connector C, which in this exemplary embodiment

is shown as a component of Delivery Segment DS, but alternate configurations are within the scope of the present invention. Also shown are hidden line views of the Housing H, Delivery Segment DSx, and Connector C that reveal details of an embodiment, such as Circuit Board CBx, Light Source LSx, Optical Lens OLx, the proximal portion of the Delivery Segment DSx, and a Hermetic Barrier HBx. Light Source LSx may be mounted to and electrical delivered thereto by Circuit Board CBx. Optical Lens OLx may be a sapphire rod lens that serves to transmit light to Delivery Segment DSx.

Figure 58 shows an enlarged view of the implantable Housing H and the optical feed-through OFT, comprised of the Optical Lens OLx and the Flanged Seal FSx. In an exemplary embodiment, the outer cylindrical surface of the sapphire lens may be coated with high purity gold, for example, and brazed to a flanged seal, such as a titanium seal, in a brazing furnace. This may create a biocompatible hermetic connection between Optical Lens OLx and the Flanged Seal FSx. The exemplary lens-seal combination may then be inserted into a hole in the outer surface of Housing H, which may also be comprised of titanium, and Flanged Seal FSx welded at least partially about the perimeter of a complementary hole in Housing H. This may create a completely biocompatible hermetically sealed assembly through which light from Light Source LSx may be coupled from within Housing H and transmit light outside of Housing H for use by Delivery Segments DS, and/or an Applicator A for treatment at a target tissue, as has been described elsewhere herein.

Figure 59 shows an isometric view of an embodiment of the present invention, in which Light Source LSx may be at least partially optically coupled to fiber bundle FBx via Optical Lens OLx interposed between the two. Optically index-matched adhesive

may be used to affix Optical Lens OLx onto Light Source LSx directly. It should be understood that the light source may be contained within a hermetically sealed implantable housing, not shown for clarity, and that Optical Lens OLx crosses the wall of the hermetically sealed implantable Housing H wherein a portion of Optical Lens OLx resides within Housing H and another portion of Optical Lens OLx resides outside of Housing H and is hermetically sealed around at least a portion of its Outer Surface OS, and that a Fiber Bundle FB may reside outside the hermetically sealed implantable Housing H and may be coupled to Optical Lens OLx. For instance, if a single source Light Source LS is used, such as an LED, a bundle of 7 Optical Fibers OFx may be used to capture the output of Light Source LS, which may be, for example, a 1mm x 1mm LED. Fiber Bundle FB may have an outer diameter of 1mm to assure that all Optical Fibers OFx are exposed to the output of Light Source LS. Using fibers of 0.33mm outer (cladding) diameter is the most efficient way of packing 7 fibers into a circular cross section using a hexagonal close-packed (HCP) configuration to approximate a 1mm diameter circle. The ultimate optical collection efficiency will scale from the filling ratio, the square of the fiber core/cladding ratio, and in further proportion to the ratio of the fiber étendue to that of the LED output as the numerical apertures are considered. These sub-fibers, or sub-bundles as the case may be, may be separated and further routed, trimmed, cut, polished, and/or lensed, depending upon the desired configuration. Brazing of Optical Lens OLx and the Flanged Seal FSx should be performed prior to the use of adhesives.

Number of Fibers	Circular Filling %	Square Filling %
7	78	61
19	80	63
37	81	63.5
55	81.5	64
85	82	64.5

The above table describes several different possibilities for coupling light from a single source into a plurality of fibers (a bundle) in a spatially efficient manner. For circular fibers, the HCP configuration has a maximum filling ratio of ~90.7%. It should be understood that even more efficient bundles may be constructed using hexagonal or otherwise shaped individual fibers and the Fiber Bundles FBx shown are merely for exemplary purposes. The plurality of fibers may be separated into smaller, more flexible sub-bundles. Fiber Bundles FBx may be adhesively bonded together and/or housed within a sheath, not shown for clarity. Multiple smaller Optical Fibers OFx may be used to provide an ultimately more flexible Fiber Bundle FBx, and may be flexibly routed through tortuous pathways to access target tissue. Additionally, Optical Fibers OFx may be separated either individually or in sub groups to be routed to more than one target tissue site. For instance, if a seven fiber construct is used, these seven fibers may be routed to seven individual targets. Similarly, if a 7x7 construction is used, the individual bundles of 7 fibers may be similarly routed to seven individual targets and may be more flexible than the

alternative 1 x 7 construct fiber bundle and hence routed to the target more easily.

Figure 60 illustrates an embodiment of the present invention, wherein an Applicator A may be used to illuminate a target tissue N with using at least one Light Source LSx. Light Source(s) LSx may be LEDs or laser diodes. Light Source(s) LSx may be located at or adjacent to the target tissue, and reside at least partially within an Applicator A, and be electrically connected by Delivery Segment(s) DS to their power supply and controller that reside, for example, inside a Housing H.

Figure 61 shows such an exemplary system configuration. In this illustrative embodiment, a single strip of LEDs is encased in an optically clear and flexible silicone, such as the low durometer, unrestricted grade implantable materials MED-4714 or MED4-4420 from NuSil, by way of non-limiting examples. This configuration provides a relatively large surface area for the dissipation of heat. For example, a 0.2mm x 0.2mm 473nm wavelength LED, such as those used in the picoLED devices by Rohm, or the die from the Luxeon Rebel product available from Phillips, Inc., may produce about 1.2mW of light. In the exemplary embodiment being described, there are 25 LEDs utilized, producing a total of about 30mW of light, and in turn generate about 60mW of heat. They are nominally between 30-50% efficient. The heat generated by the LEDs may be dissipated over the relatively large surface area afforded by the present invention of 15mm^2, or a heat flux of 4mW/mm^2 at the surface of Applicator A. Implantable (unrestricted) grade silicone has a thermal conductivity of about 0.82$Wm^{-1}K^{-1}$, and a thermal diffusivity of about 0.22mm^2s^{-1} and distributing the heat over a larger area and/or volume of this material decreases the peak temperature rise produced at the tissue surface.

Figure 62 illustrates an alternate configuration of the embodiment of Figure 60, with the addition of a spiral, or helical design for Applicator A is utilized. Such a configuration may allow for greater exposure extent of the target tissue. This may also be useful to allow slight misplacement of the applicator with respect to the target tissue, if the longitudinal exposure length is greater than that intended for the target tissue and the deployed location of Applicator A also subsumes the target tissue by a reasonable margin. A reasonable margin for most peripheral applications is about ±2mm. Applicator A must provide an inner diameter (ID) that is at least slightly larger than the outer diameter (OD) of the target tissue for the target tissue with Applicator A to move axially without undue stress. Slightly larger in the case of most peripheral nerves may provide that the ID of Applicator A be 5-10% larger than the target tissue OD.

Fiber and or protective coverings on or containing a waveguide, such as, but not limited to optical fiber may be shaped to provide a strain-relieving geometry such that forces on the applicator are much reduced before they are transmitted to the target tissue. By way of non-limiting example, shapes for a flexible fiber to reduce forces on the target tissue include; serpentine, helical, spiral, dual non-overlapping spiral (or "bowtie"), cloverleaf, or any combination of these.

Figures 63A-63D illustrate a few of these different configurations in which Undulations U are configured to create a strain relief section of optical waveguide Delivery Segment DS prior to its connection to Applicator A via Connector C. Figure 63A illustrates a Serpentine section of Undulations U for creating a strain relief section within Delivery Segment DS and/or Applicator A. Figure 63B illustrates a Helical section

of Undulations U for creating a strain relief section within Delivery Segment DS and/or Applicator A. Figure 63C illustrates a Spiral section of Undulations U for creating a strain relief section within Delivery Segment DS and/or Applicator A. Figure 63D illustrates a Bowtie section of Undulations U for creating a strain relief section within Delivery Segment DS and/or Applicator A. Target Tissue resides within Applicator in these exemplary embodiments, but other configurations, as have been described elsewhere herein, are also within the scope of the present invention.

Figure 64 shows an alternate embodiment, wherein Applicator A may be configured such that it is oriented at an angle relative the Delivery Segment DS, and not normal to it as was illustrated in the earlier exemplary embodiments. Such an angle might be required, for example, in order to accommodate anatomical limitations, such as the target tissue residing in a crevice or pocket, as may the case for certain peripheral nerves. Another bend, or Undulation U, in either the Delivery Segment DS or in an element of Applicator A, such as an output coupler, as has been described elsewhere herein, may be utilized to create the angle.

In an alternate embodiment, an optical feature may be incorporated into the system at the distal end of the Delivery Segment DS, or the proximal end of the optical input of Applicator A to reflect the light an angle relative to the direction of the fiber to achieve the angle.

Plastic optical fiber such as 100μm core diameter ESKA SK-10 from Mitsubishi may be routed and/or shaped in a jig and then heat-set to form Undulations U directly. Alternately, a covering may be used over the waveguide, and that covering may be fabricated to create Undulations U in the waveguide

indirectly. An alternate exemplary plastic fiber waveguide may be constructed from a PMMA (n=1.49) core material with a cladding of THV (n-1.35) to provide an NA of 0.63. A polyethylene tube, such as, PE10 from Instech Solomon, may be used as a cover, shaped in a jig and heat-set to create Undulations U while using a silica optical fiber within the tube. Heat-setting for these two exemplary embodiments may be accomplished by routing the element to be shaped in a jig or tool to maintain the desired shape, or one approximating it, and then heating the assembly in an oven at 70°C for 30 minutes. Alternately, the bends may be created in more gradual steps, such that only small bends are made at each step and the final heating (or annealing) provides the desired shape. This approach may better assure that no stress-induced optical changes are engendered, such as refractive index variations, which might result in transmission loss. Although optical fiber has been discussed in the previous examples, other delivery segment and applicator configurations are within the scope of the present invention.

Light transmission through tissue such as skin is diffusive, and scattering the dominant process. Scattering diminishes the directionality and brightness of light illuminating tissue. Thus, the use of highly directional and/or bright sources is rendered moot. This may limit the depth in tissue that a target may be affected. An in-vivo light collector may be used within the tissue of a patient in cases where straightforward transcutaneous illumination cannot be used to adequately irradiate a target due to irradiance reduction, and a fully implanted system may be deemed too invasive.

In one embodiment, an at least partially implanted system for collecting light from an external source may be placed in-

vivo and/or in-situ within the skin of a patient to capture and transmit light between the external light source and an implanted applicator. Such applicators have been described elsewhere herein.

Alternately, an at least partially implanted system for collecting light from an external source may be placed in-vivo and/or in-situ within the skin of a patient to capture and transmit light between the external light source and direct it to the target tissue directly, without the use of a separate applicator.

The light collection element of the system may be constructed, for example, from a polymer material that has an outer layer of a nominally different index of refraction than that of the body or core material, such as is done in fiber optics. While the index of refraction of skin and other tissues is about equal to that of water, corresponding to a range of 1.33 - 1.40 in the visible spectrum, and would provide a functional cladding that may yield an NA as high as 0.56 when PMMA is used is the unclad core material. However, native chromophores within tissues such as skin that may be avid absorbers of the light from the external light source, especially visible light. Examples of such native chromophores are globins (e.g. oxy-, deoxy-, and met-hemoglobin), melanins (e.g. neuro-, eu-, and pheo-melanin), and xanthophylls (e.g. carotenol fatty acid esters). The evanescent wave present in an insufficiently clad or unclad collection device may be coupled into absorption by these native pigments that potentially causes unintended and/or collateral heating that not only diminishes the amount of light conducted to the target, but also may create a coating on the collector that continually degrades its performance. For example, there may be melanin

resident at the dermal-epidermal junction, and blood resident in the capillary bed of the skin.

In one embodiment, the depth of the surface of the implantable light conductor is placed between 100 and 1000μm beneath the tissue surface. In the case of cutaneous implantation, this puts that surface below the epidermis.

The implantable light collector/conductor may be made of polymeric, glass, or crystalline material. Some non-limiting examples are; PMMA, Silicones, such as MED-4714 or MED4-4420 from NuSil, PDMS, and High-Refractive-Index Polymers (HRIPs), as are described elsewhere herein.

A cladding layer may also be used on the implantable light collector to improve reliability, robustness and overall performance. By way of non-limiting example, THV (a low index fluoropolymer blend), Fluorinated ethylene propylene (FEP), and/or polymethylpentene may be used to construct cladding layers about a core material. These materials are biocompatible and possess relatively low indices of refraction (n=1.35-1.4). Thus, they provide for light collection over a wide numerical aperture (NA).

In addition to the use of a cladding layer on the implantable light conductor/collector, a coating may be disposed to the outer surface of the conductor/collector to directly confine the light within the conductor, and/or to keep the maintain the optical quality of the outer surface to avoid absorption by native chromophores in the tissue at or near the outer surface of the collector because the evanescent wave present in a waveguide may still interact with the immediate environment. Such coating might be, for example, metallic coatings, such as, Gold, Silver, Rhodium, Platinum, Aluminum. A dielectric coating may also be used. Examples being; SiO_2, Al_2O_3

for protecting a metallic coating, or a layered dielectric stack coating to improve reflectivity, or a simple single layer coating to do likewise, such as quarter-wave thickness of MgF_2.

Alternately, the outer surface of the implantable light collector may be configured to utilize a pilot member for the introduction of the device into the tissue. This pilot member may be configured to be a cutting tool and/or dilator, from which the implantable light conductor may be removably coupled for implantation.

Implantation may be performed, by way of non-limiting example, using pre-operative and/or intra-operative imaging, such as radiography, fluoroscopy, ultrasound, magnetic resonance imaging (MRI), computed tomography (CT), optical imaging, microscopy, confocal microscopy, endoscopy, and optical coherence tomography (OCT).

Alternately, the pilot member may also form a base into which the implantable light collector is retained while implanted. As such, the pilot member may be a metal housing that circumscribes the outer surface of the implantable light collector and provides at least a nominally sheltered environment. In such cases replacement of the light collector may be made easier by leaving in place the retaining member (as the implanted pilot member may be known) and exchanging the light collector only. This may be done, for example, in cases where chronic implantation is problematic and the optical quality and/or efficiency of the light collector diminishes.

Alternately, the outer surface of the implantable collector may be made more bioinert by utilizing coatings of: Gold or Platinum, parylene-C, poly(ethylene glycol) (PEG), phosphoryl choline, Polyethylene oxide polymer, self-assembled monolayers

(SAMs) of, for example, D-mannitol-terminated alkanethiols, as has been described elsewhere herein.

The collection element may be comprised of, by way of non-limiting example, an optical fiber or waveguide, a lightpipe, or plurality of such elements. For example, considering only scattering effects, a single 500μm diameter optical fiber with an intrinsic numerical aperture (NA) of 0.5 that is located 300μm below the skin surface may be able to capture at most about 2% of the light from a Ø1mm beam of collimated light incident upon the skin surface. Thus, a 1W source power may be required in order to capture 20mW, and require a surface irradiance of 1.3W/mm^2. This effect improves additively for each such fiber included in the system. For example, 4 such fibers may lower the surface incident optical power required by the same factor of 4 and still capture 20mW. Of course, this does not increase the delivered brightness at the target, but may provide for more power to be delivered and distributed at the target, such as might be done in circumferential illumination. It should be known that it is a fundamental law of physics that brightness cannot be increased without adding energy to a system. Multiple fibers, such as those described, may be used to supply light to an applicator via multiple delivery segments, as are described elsewhere herein.

Larger numbers of light collecting elements, such as the optical fiber waveguides described in the embodiments above are also within the scope of the present invention.

Similar to the embodiment of Figure 34, an alternate embodiment is shown in Figure 65. Light Rays LR from External Light Source ELS are shown in the illustrative exemplary embodiment to exit External Light Source ELS, encounter External Boundary EB (such as the skin's stratum corneum and/or epidermis

and subsequently traverse the Dermal-Epidermal Junction DEJ) to reach the proximal surface of Implantable Light Collector PLS, where the proximal collection surface is divided into individual sections that each provide input for waveguides and/or delivery segments DSx that are operatively coupled to an Applicator A in order to illuminate target tissue N.

Figure 66 illustrates an alternate embodiment similar to that of Figure 65, where Implantable Light Collector PLS is not subdivided into separate sections, but instead supplies light to Applicator A via a single input channel. Delivery Segments DSx are not shown, but may be utilized in a further embodiment.

Surface cooling techniques and apparatus may be used in further embodiments of the present invention to mitigate the risk of collateral thermal damage that may be caused by optical absorption by the melanin located at the dermal-epidermal junction. Basic skin-cooling approaches have been described elsewhere. Such as, by way on non-limiting example, those described by U.S. Pat. Nos. 5,486,172; 5,595,568; and 5,814,040; which are incorporated herein in their entirety.

Figure 67 illustrates an alternate embodiment of the present invention similar to that of Figure 66, but with the addition of Skin Cooling Element SCE. Skin Cooling Element SCE is shown in direct contact with the skin surface, but need not be, as has been described in the aforementioned incorporated patent references. Similar to External Light Source ELS, Skin Cooling Element SCE may also be connected to a system controller and power supply. The user may program the parameters of Skin Cooling Element SCE to improve comfort and efficacy by adjusting the amount and/or temperature of the cooling, as well as its duration and timing relative to the illumination light from

External Light Source ELS. External is understood to be equivalent to extracorporeal.

In an alternate embodiment, a tissue clearing agent, such as those described elsewhere herein, may be used to improve the transmission of light through tissue for collection by an implanted light collection device. The following tissue clearing agents may be used, by way of non-limiting examples; glycerol, polypropylene glycol-based polymers, polyethylene glycol-based polymers (such as PEG200 and PEG400), polydimethylsiloxane, 1,4-butanediol, 1,2-propanediol, certain radiopaque x-ray contrast media (such as Reno-DIP, Diatrizoate meglumine). For example, topical application of PEG-400 and Thiazone in a ratio of 9:1 for between 15-60 minutes may be used to decrease the scattering of light in human skin to improve the overall transmission of light via an implantable light collector.

Referring to Figure 28, a block diagram is depicted illustrating various components of an example implantable housing H. In this example, implantable stimulator includes processor CPU, memory MEM, power supply PS, telemetry module TM, antenna ANT, and the driving circuitry DC for an optical stimulation generator (which may or may not include a light source, as is described elsewhere herein). The Housing H is coupled to one Delivery Segments DSx, although it need not be. It may be a multi-channel device in the sense that it may be configured to include multiple optical paths (e.g., multiple light sources and/or optical waveguides or conduits) that may deliver different optical outputs, some of which may have different wavelengths. More or less delivery segments may be used in different implementations, such as, but not limited to, one, two, five or more optical fibers and associated light

sources may be provided. The delivery segments may be detachable from the housing, or be fixed.

Memory (MEM) may store instructions for execution by Processor CPU, optical and/or sensor data processed by sensing circuitry SC, and obtained from sensors both within the housing, such as battery level, discharge rate, etc., and those deployed outside of the Housing (H), possibly in Applicator A, such as optical and temperature sensors, and/or other information regarding therapy for the patient. Processor (CPU) may control Driving Circuitry DC to deliver power to the light source (not shown) according to a selected one or more of a plurality of programs or program groups stored in Memory (MEM). The Light Source may be internal to the housing H, or remotely located in or near the applicator (A), as previously described. Memory (MEM) may include any electronic data storage media, such as random access memory (RAM), read-only memory (ROM), electronically-erasable programmable ROM (EEPROM), flash memory, etc. Memory (MEM) may store program instructions that, when executed by Processor (CPU), cause Processor (CPU) to perform various functions ascribed to Processor (CPU) and its subsystems, such as dictate pulsing parameters for the light source.

Electrical connections may be through Housing H via an Electrical Feedthrough EFT, such as, by way of non-limiting example, The SYGNUS® Implantable Contact System from Bal-SEAL.

In accordance with the techniques described in this disclosure, information stored in Memory (MEM) may include information regarding therapy that the patient had previously received. Storing such information may be useful for subsequent treatments such that, for example, a clinician may retrieve the stored information to determine the therapy applied to the

patient during his/her last visit, in accordance with this disclosure. Processor CPU may include one or more microprocessors, digital signal processors (DSPs), application-specific integrated circuits (ASICs), field-programmable gate arrays (FPGAs), or other digital logic circuitry. Processor CPU controls operation of implantable stimulator, e.g., controls stimulation generator to deliver stimulation therapy according to a selected program or group of programs retrieved from memory (MEM). For example, processor (CPU) may control Driving Circuitry DC to deliver optical signals, e.g., as stimulation pulses, with intensities, wavelengths, pulse widths (if applicable), and rates specified by one or more stimulation programs. Processor (CPU) may also control Driving Circuitry (DC) to selectively deliver the stimulation via subsets of Delivery Segments (DSx), and with stimulation specified by one or more programs. Different delivery segments (DSx) may be directed to different target tissue sites, as was previously described.

Power supply (PS) may include a battery, such as, by way of non-limiting example, a rechargeable Li-ion or Li-Polymer battery. One such suitable cell is the LP-503455 from Li-Pol.

Telemetry module (TM) may include, by way of non-limiting example, a radio frequency (RF) transceiver to permit bi-directional communication between implantable stimulator and each of a clinician programmer module and/or a patient programmer module (generically a clinician or patient programmer, or "C/P"). A more generic form is described above in reference to Figure 2 as the input/output (I/O) aspect of a controller configuration (P/C). Telemetry module (TM) may include an Antenna (ANT), of any of a variety of forms. For example, Antenna (ANT) may be formed by a conductive coil or

wire embedded in a housing associated with medical device. Alternatively, antenna (ANT) may be mounted on a circuit board carrying other components of implantable stimulator or take the form of a circuit trace on the circuit board. In this way, telemetry module (TM) may permit communication with a programmer (C/P). Given the energy demands and modest data-rate requirements, the Telemetry system may be configured to use inductive coupling to provide both telemetry communications and power for recharging, although a separate recharging circuit (RC) is shown in Figure 28 for explanatory purposes. An alternate configuration is shown in Figure 29.

Referring to Figure 29, a telemetry carrier frequency of 175kHz aligns with a common ISM band and may use on-off keying at 4.4kbps to stay well within regulatory limits. Alternate telemetry modalities are discussed elsewhere herein. The uplink may be an H-bridge driver across a resonant tuned coil. The telemetry capacitor, C1, may be placed in parallel with a larger recharge capacitor, C2, to provide a tuning range of 50-130 kHz for optimizing the RF-power recharge frequency. Due to the large dynamic range of the tank voltage, the implementation of the switch, S1, employs a nMOS and pMOS transistor connected in series to avoid any parasitic leakage. When the switch is OFF, the gate of pMOS transistor is connected to battery voltage, VBattery, and the gate of nMOS is at ground. When the switch is ON, the pMOS gate is at negative battery voltage, - VBattery, and the nMOS gate is controlled by charge pump output voltage. The ON resistance of the switch is designed to be less than 5Ω to maintain a proper tank quality factor. A voltage limiter, implemented with a large nMOS transistor, may be incorporated in the circuit to set the full wave rectifier output slightly

higher than battery voltage. The output of the rectifier may then charge a rechargeable battery through a regulator.

Figure 30 relates to an embodiment of the Driving Circuitry DC, and may be made to a separate integrated circuit (or "IC"), or application specific integrated circuit (or "ASIC"), or a combination of them.

The control of the output pulse train, or burst, may be managed locally by a state-machine, as shown in this non-limiting example, with parameters passed from the microprocessor. Most of the design constraints are imposed by the output drive DAC. First, a stable current is required to reference for the system. A constant current of 100 nA, generated and trimmed on chip, is used to drive the reference current generator, which consists of an R-2Rbased DAC to generate an 8-bit reference current with a maximum value of 5 A. The reference current is then amplified in the current output stage with the ratio of R_O and R_{ref}, designed as a maximum value of 40. An on-chip sense-resistor-based architecture was chosen for the current output stage to eliminate the need to keep output transistors in saturation, reducing voltage headroom requirements to improve power efficiency. The architecture uses thin-film resistors (TFRs) in the output driver mirroring to enhance matching. To achieve accurate mirroring, the nodes X and Y may be forced to be the same by the negative feedback of the amplifier, which results in the same voltage drop on R_O and R_{ref}. Therefore, the ratio of output current, I_O, and the reference current, I_{ref}, equals to the ratio of and R_{ref} and R_O.

The capacitor, C, retains the voltage acquired in the precharge phase. When the voltage at Node Y is exactly equal to the earlier voltage at Node X, the stored voltage on C biases the gate of P2 properly so that it balances I_{bias}. If, for

example, the voltage across R_O is lower than the original R_{ref} voltage, the gate of P2 is pulled up, allowing I_{bias} to pull down on the gate on P1, resulting in more current to R_O. In the design of this embodiment, charge injection is minimized by using a large holding capacitor of 10pF. The performance may be eventually limited by resistor matching, leakage, and finite amplifier gain. With 512 current output stages, the optical stimulation IC may drive two outputs for activation and inhibition (as shown in Figure 30) with separate sources, each delivering a maximum current of 51.2mA.

Alternatively, if the maximum back-bias on the optical element can withstand the drop of the other element, then the devices can be driven in opposite phases (one as sinks, one as sources) and the maximum current exceeds 100mA. The stimulation rate can be tuned from 0.153Hz to 1kHz and the pulse or burst duration(s) can be tuned from 100s to 12ms. However, the actual limitation in the stimulation output pulse-train characteristic is ultimately set by the energy transfer of the charge pump, and this generally should be considered when configuring the therapeutic protocol.

The Housing H (or applicator, or the system via remote placement) may further contain an accelerometer to provide sensor input to the controller resident in the housing. This may be useful for modulation and fine control. Remote placement of an accelerometer may be made at or near the anatomical element under optogenetic control, and may reside within the applicator, or nearby it. In times of notable detected motion, the system may alter it programming to accommodate the patient's intentions and provide more or less stimulation and/or inhibition, as is required for the specific case at hand.

The Housing H may still further contain a fluidic pump (not shown) for use with the applicator, as was previously described herein.

External programming devices for patient and/or physician can be used to alter the settings and performance of the implanted housing. Similarly, the implanted apparatus may communicate with the external device to transfer information regarding system status and feedback information. This may be configured to be a PC-based system, or a stand-alone system. In either case, the system generally should communicate with the housing via the telemetry circuits of Telemetry Module (TM) and Antenna (ANT). Both patient and physician may utilize controller/programmers (C/P) to tailor stimulation parameters such as duration of treatment, optical intensity or amplitude, pulse width, pulse frequency, burst length, and burst rate, as is appropriate.

Once the communications link (CL) is established, data transfer between the MMN programmer/controller and the housing may begin. Examples of such data are:

1. From housing to controller/programmer:
    a. Patient usage
    b. Battery lifetime
    c. Feedback data
        i. Device diagnostics

2. From controller/programmer to housing:

a. Updated illumination level settings based upon device diagnostics
b. Alterations to pulsing scheme
c. Reconfiguration of embedded circuitry
    i. such as field programmable gate array (FPGA), application specific integrated circuit (ASIC), or other integrated or embedded circuitry

By way of non-limiting examples, near field communications, either low power and/or low frequency; such as ZigBee, may be employed for telemetry. The tissue(s) of the body have a well-defined electromagnetic response(s). For example, the relative permittivity of muscle demonstrates a monotonic log-log frequency response, or dispersion. Therefore, it is advantageous to operate an embedded telemetry device in the frequency range of ≤1GHz. In 2009 (and then updated in 2011), the US FCC dedicated a portion of the EM Frequency spectrum for the wireless biotelemetry in implantable systems, known as The Medical Device Radiocommunications Service (known as "MedRadio"). Devices employing such telemetry may be known as "medical micropower networks" or "MMN" services. The currently reserved spectra are in the 401 - 406, 413 - 419, 426 - 432, 438 - 444, and 451 - 457 MHz ranges, and provide for these authorized bandwidths:

- 401 - 401.85 MHz: 100 kHz
- 401.85 - 402 MHz: 150 kHz
- 402 - 405 MHz: 300 kHz
- 405 - 406 MHz: 100 kHz
- 413 - 419 MHz: 6 MHz
- 426 - 432 MHz: 6 MHz
- 438 - 444 MHz: 6 MHz
- 451 - 457 MHz: 6 MHz

The rules do not specify a channeling scheme for MedRadio devices. However, it should be understood that the FCC stipulates that:

- MMNs should not cause harmful interference to other authorized stations operating in the 413-419 MHz, 426-432 MHz, 438-444 MHz, and 451-457 MHz bands.
- MMNs must accept interference from other authorized stations operating in the 413-419 MHz, 426-432 MHz, 438-444 MHz, and 451-457 MHz bands.
- MMN devices may not be used to relay information to other devices that are not part of the MMN using the 413-419 MHz, 426-432 MHz, 438-444 MHz, and 451-457 MHz frequency bands.

- An MMN programmer/controller may communicate with a programmer/controller of another MMN to coordinate sharing of the wireless link.
- Implanted MMN devices may only communicate with the programmer/controller for their MMN.
- An MMN implanted device may not communicate directly with another MMN implanted device.
- An MMN programmer/controller can only control implanted devices within one patient.

Interestingly, these frequency bands are used for other purposes on a primary basis such as Federal government and private land mobile radios, Federal government radars, and remote broadcast of radio stations. It has recently been shown that higher frequency ranges are also applicable and efficient for telemetry and wireless power transfer in implantable medical devices.

An MMN may be made not to interfere or be interfered with by external fields by means of a magnetic switch in the implant itself. Such a switch may be only activated when the MMN programmer/controller is in close proximity to the implant. This also provides for improved electrical efficiency due to the restriction of emission only when triggered by the magnetic switch. Giant Magnetorestrictive (GMR) devices are available with activation field strengths of between 5 and 150 Gauss. This is typically referred to as the magnetic operate point. There is intrinsic hysteresis in GMR devices, and they also

exhibit a magnetic release point range that is typically about one-half of the operate point field strength. Thus, a design utilizing a magnetic field that is close to the operate point will suffer from sensitivities to the distance between the housing and the MMN programmer/controller, unless the field is shaped to accommodate this. Alternately, one may increase the field strength of the MMN programmer/controller to provide for reduced sensitivity to position/distance between it and the implant. In a further embodiment, the MMN may be made to require a frequency of the magnetic field to improve the safety profile and electrical efficiency of the device, making it less susceptible to errant magnetic exposure. This can be accomplished by providing a tuned electrical circuit (such as an L-C or R-C circuit) at the output of the switch.

Alternately, another type of magnetic device may be employed as a switch. By way of non-limiting example, a MEMS device may be used. A cantilevered MEMS switch may be constructed such that one member of the MEMS may be made to physically contact another aspect of the MEMS by virtue of its magnetic susceptibility, similar to a miniaturized magnetic reed switch. The suspended cantilever may be made to be magnetically susceptible by depositing a ferromagnetic material (such as, but not limited to Ni, Fe, Co, NiFe, and NdFeB) atop the end of the supported cantilever member. Such a device may also be tuned by virtue of the cantilever length such that it only makes contact when the oscillations of the cantilever are driven by an oscillating magnetic field at frequencies beyond the natural resonance of the cantilever.

Alternately, an infrared-sensitive switch might be used. In this embodiment of this aspect of the present invention, a photodiode or photoconductor may be exposed to the outer surface

of the housing and an infrared light source used to initiate the communications link for the MMN. Infrared light penetrates body tissues more readily than visible light due to its reduced scattering. However, water and other intrinsic chromophores have avid absorption, with peaks at 960, 1180, 1440, and 1950nm, as are shown in the spectra of Figure 31 (1018), where the water spectrum runs form 700-2000nm and that of adipose tissue runs from 600-1100nm.

However, the penetration depth in tissue is more influenced by its light scattering properties, as shown in the spectrum of Figure 32 (1020), which displays the optical scattering spectrum for human skin, including the individual components from both Mie (elements of similar size to the wavelength of light) and Rayleigh (elements of smaller size than the wavelength of light) scattering effects.

This relatively monotonic reduction in optical scattering far outweighs absorption, when the abovementioned peaks are avoided. Thus, an infrared (or near-infrared) transmitter operating within the range of 800 - 1300nm may be preferred. This spectral range is known as the skin's "optical window."

Such a system may further utilize an electronic circuit, such as that shown in Figure 33 (1022), for telemetry, and not just a sensing switch. Based upon optical signaling, such a system may perform at high data throughput rates.

Generically, the signal-to-noise ratio (SNR) of a link is defined as,

$$SNR_i = \frac{I_s}{I_N} = \frac{P_s R}{I_{N_{shot}} + P_{N_{amb}} R}$$

where I_S and I_N are the photocurrents resulting from incident signal optical power and photodiode noise current respectively, P_S is the received signal optical power, R is the photodiode responsivity (A/W), I_{Nelec} is the input referred noise for the receiver and P_{Namb} is the incident optical power due to interfering light sources (such as ambient light).

P_S can be further defined as

$$P_S = \int_{A_T} P_{Tx} J_{Rx\lambda} \eta_\lambda dA$$

where P_{Tx} (W) is the optical power of the transmitted pulse, $J_{Rx\lambda}$ (cm^{-2}) is the tissue's optical spatial impulse response flux at wavelength λ, η_λ is an efficiency factor ($\eta_\lambda \leq 1$) accounting for any inefficiencies in optics/optical filters at λ and A_T represents the tissue area over which the receiver optics integrate the signal.

The abovementioned factors that affect the total signal photocurrent and their relationship to system level design parameters include emitter wavelength, emitter optical power, tissue effects, lens size, transmitter-receiver misalignment, receiver noise, ambient light sources, photodiode responsivity, optical domain filtering, receiver signal domain filtering, line coding and photodiode and emitter selection. Each of these parameters can be independently manipulated to ensure that the proper signal strength for a given design will be achieved.

Most potentially-interfering light sources have signal power that consists of relatively low frequencies (e.g. Daylight: DC; Fluorescent lights: frequencies up to tens or hundreds of kilohertz), and can therefore be rejected by using a high-pass filter in the signal domain and using higher frequencies for data transmission.

The emitter may be chosen from the group consisting of, by way of non-limiting example, a VCSEL, an LED, a HCSEL. VCSELs are generally both higher brightness and more energy efficient than the other sources and they are capable of high-frequency modulation. An example of such a light source is the device sold under the model identifier "HFE 4093-342" from Finisar, Inc., which operates at 860nm and provides ≤5mW of average power. Other sources are also useful, as are a variety of receivers (detectors). Some non-limiting examples are listed in the following table.

820-850 nm	Agilent HFBR-1412 Agilent HFBR-1416 Hamamatsu L1915 Hamamatsu L5128 Hamamatsu L5871 Hamamatsu L6486	Agilent HFBR-2412 Agilent HFBR-2416 Hamamatsu GT4176
950 nm	Infineon SFH 4203 Infineon SFH 4301 Infineon SFH 4502 Infineon SFH 4503	Infineon SFH 203 Infineon SFH 5400 Infineon SFH 5440 Infineon SFH5441
1300 nm	Agilent HFBR-1312 Hamamatsu L7866 Hamamatsu L7850	Agilent HFBR-2316

Alignment of the telemetry emitter to receiver may be improved by using a non-contact registration system, such as an array of coordinated magnets with the housing that interact with

sensors in the controller/programmer to provide positional information to the user that the units are aligned. In this way, the overall energy consumption of the entire system may be reduced.

Although glycerol and polyethylene glycol (PEG) reduce optical scattering in human skin, their clinical utility has been very limited. Penetration of glycerol and PEG through intact skin is very minimal and extremely slow, because these agents are hydrophilic and penetrate the lipophilic stratum corneum poorly. In order to enhance skin penetration, these agents need to be either injected into the dermis or the stratum corneum has to be removed, mechanically (e.g., tape stripping, light abrasion) or thermally (e.g., erbium: yttrium-aluminum-garnet (YAG) laser ablation), etc. Such methods include tape stripping, ultrasound, iontophoresis, electroporation, microdermabrasion, laser ablation, needle-free injection guns, and photomechanically driven chemical waves (such as the process known as "optoporation"). Alternately, microneedles contained in an array or on a roller (such as the Dermaroller® micro-needling device) may be used to decrease the penetration barrier. The Dermaroller® micro-needling device is configured such that each of its 192 needles has a 70μm diameter and 500μm height. These microneedles are distributed uniformly atop a 2cm wide by 2cm diameter cylindrical roller. Standard use of the microneedle roller typically results in a perforation density of 240 perforations/cm^2 after 10 to 15 applications over the same skin area. While such microneedle approaches are certainly functional and worthwhile, clinical utility would be improved if the clearing agent could simply be applied topically onto intact skin and thereafter migrate across the stratum corneum and epidermis into the dermis. Food and Drug Administration (FDA)

approved lipophilic polypropylene glycol-based polymers (PPG) and hydrophilic PEG-based polymers, both with indices of refraction that closely match that of dermal collagen (n=1.47) are available alone and in a combined pre-polymer mixture, such as polydimethylsiloxane (PDMS). PDMS is optically clear, and, in general, is considered to be inert, non-toxic and non-flammable. It is occasionally called dimethicone and is one of several types of silicone oil (polymerized siloxane), as was described in detail in an earlier section. The chemical formula for PDMS is $CH_3[Si(CH_3)_2O]_nSi(CH_3)_3$, where n is the number of repeating monomer $[SiO(CH_3)_2]$ units. The penetration of these optical clearing agents into appropriately treated skin takes about 60 minutes to achieve a high degree of scattering reduction and commensurate optical transport efficiency. With that in mind, a system utilizing this approach may be configured to activate its illumination after a time sufficient to establish optical clearing, and in sufficient volume to maintain it nominally throughout or during the treatment exposure. Alternately, the patient/user may be instructed to treat their skin a sufficient time prior to system usage.

Alternately, the microneedle roller may be configured with the addition of central fluid chamber that may contain the tissue clearing agent, which is in communication with the needles. This configuration may provide for enhanced tissue clearing by allowing the tissue clearing agent to be injected directly via the microneedles.

A compression bandage-like system could push exposed emitters and/or applicators into the tissue containing a subsurface optogenetic target to provide enhanced optical penetration via pressure-induced tissue clearing in cases where the applicator is worn on the outside of the body; as might be

the case with a few of the clinical indications described herein, like micromastia, erectile dysfunction, and neuropathic pain. This configuration may also be combined with tissue clearing agents for increased effect. The degree of pressure tolerable is certainly a function of the clinical application and the site of its disposition. Alternately, the combination of light source compression into the target area may also be combined with an implanted delivery segment, or delivery segments, that would also serve to collect the light from the external source for delivery to the applicator(s). Such an example is shown in Figure 34, where External Light Source PLS (which may the distal end of a delivery segment, or the light source itself) is placed into contact with the External Boundary EB of the patient. The PLS emits light into the body, which it may be collected by Collection Apparatus CA, which may be a lens, a concentrator, or any other means of collecting light, for propagation along Trunk Waveguide TWG, which may a bundle of fibers, or other such configuration, which then bifurcates into separate interim delivery segments BNWGx, that in turn deliver the light to Applicators Ax that are in proximity to Target N.

Figure 68 illustrates an embodiment, where an external charging device is mounted onto clothing for simplified use by a patient, comprising a Mounting Device MOUNTING DEVICE, which may be selected from the group consisting of, but not limited to: a vest, a sling, a strap, a shirt, and a pant. Mounting Device MOUNTING DEVICE further comprising a Wireless Power Transmission Emission Element EMIT, such as, but not limited to, a magnetic coil, or electrical current carrying plate, that is located substantially nearby an implanted power receiving module, such as is represented by the illustrative example of Housing H, which is configured to be operatively coupled to Delivery

Segment(s) DS. Within Housing H, may be a power supply, light source, and controller, such that the controller activates the light source by controlling current thereto. Alternately, the power receiving module may be located at the applicator (not shown), especially when the Applicator is configured to contain a Light Source.

Nerve stimulation, such as electrical stimulation ("e-stim"), may cause bidirectional impulses in a neuron, which may be characterized as antidromic and/or orthodromic stimulation. That is, an action potential may trigger pulses that propagate in both directions along a neuron. However, the coordinated use of optogenetic inhibition in combination with stimulation may allow only the intended signal to propagate beyond the target location by suppression or cancellation of the errant signal using optogenetic inhibition. This may be achieved in multiple ways using what we will term "multi-applicator devices" or "multi-zone devices". The function and characteristics of the individual elements utilized in such devices were defined earlier.

In a first embodiment, a multi-applicator device is configured to utilize separate applicators Ax for each interaction zone Zx along the target nerve N, as is shown in Figure 35. One example is the use optogenetic applicators on both ends (A1, A3) and an electrical stimulation device (A2) in the middle. This example was chosen to represent a generic situation wherein the desired signal direction may be on either side of the excitatory electrode. The allowed signal direction may be chosen by the selective application of optogenetic inhibition from the applicator on the opposite side of the central Applicator A2. In this non-limiting example, the Errant Impulse EI is on the RHS of the stimulation cuff A2, traveling

to the right, as indicated by arrow DIR-EI, and passing through the portion f the target covered by A3 and the Desired Impulse DI is on the LHS of A2, travelling to the left, as indicated by arrow DIR-DI, and, passing through the portion f the target covered by A1. Activation of A3 may serve to disallow transmission of EI via optogenetic inhibition of the signal, suppressing it. Similarly, activation of A1 instead of A3 would serve to suppress the transmission of the Desired Impulse DI and allow the Errant Impulse EI to propagate. Therefore, bi-directionality is maintained in this triple applicator configuration, making it a flexible configuration for Impulse direction control. Such flexibility may not always be clinically required, and simpler designs may be used, as is explained in subsequent paragraphs. This inhibition/suppression signal may accompany or precede the electrical stimulation, as dictated by the specific kinetics of the therapeutic target.

Each optical applicator may also be made such that it is capable of providing both optogenetic excitation and inhibition by utilizing two spectrally distinct light sources to activate their respective opsins in the target. In this embodiment, each applicator, Ax, is served by its own Delivery Segment, DSx. These Delivery Segments, DS1, DS2, and DS3 serve as conduits for light and/or electricity, as dictated by the type of applicator present. As previously described, the Delivery Segment(s) connect(s) to a Housing containing the electrical and/or electro-optical components required to provide for power supply, processing, feedback, telemetry, etc. Alternately, Applicator A2 may be an optogenetic applicator and either Applicators A1 or A3 may be used to suppress the errant signal direction.

Alternately, as mentioned above, only a pair of applicators may be required when the therapy dictates that only a single

direction is required. Referring to the embodiment of Figure 36, the directionality of the Desired Impulse DI and Errant Impulse EI described above is maintained. However, Applicator A3 is absent because the directionality of the Desired Impulse DI is considered to be fixed as leftward, and Applicator A2 is used for optogenetic suppression of the Errant Impulse EI, as previously described.

Alternately, referring to the embodiment of Figure 37, a single applicator may be used, wherein the electrical and optical activation zones Z1, Z2, and Z3 are spatially separated, but still contained within a single applicator A.

Furthermore, the combined electrical stimulation and optical stimulation described herein may also be used for intraoperative tests of inhibition in which an electrical stimulation is delivered and inhibited by the application of light to confirm proper functioning of the implant and optogenetic inhibition. This may be performed using the applicators and system previously described for testing during the surgical procedure, or afterwards, depending upon medical constraints and/or idiosyncrasies of the patient and/or condition under treatment. The combination of a multiple-applicator, or multiple-zone applicator, or multiple applicators, may also define which individual optical source elements within said applicator or applicators may be the most efficacious and/or efficient means by which to inhibit nerve function. That is, an e-stim device may be used as a system diagnostic tool to test the effects of different emitters and/or applicators within a multiple emitter, or distributed emitter, system by suppressing, or attempting to suppress, the induced stimulation via optogenetic inhibition using an emitter, or a set of emitters and ascertaining, or measuring, the patient, or

target, response(s) to see the optimal combination for use. That optimal combination may then be used as input to configure the system via the telemetric link to the housing via the external controller/programmer. Alternately, the optimal pulsing characteristics of a single emitter, or set of emitters, may be likewise ascertained and deployed to the implanted system.

In one embodiment, a system may be configured such that both the inhibitory and excitatory probes and/or applicators are both optical probes used to illuminate cells containing light-activatable ion channels that reside within a target tissue. In this configuration, the cells may be modified using optogenetic techniques, such as has been described elsewhere herein.

One further embodiment of such a system may be to attach an optical applicator, or applicators, on the Vagus nerve to send ascending stimulatory signals to the brain, while suppressing the descending signals by placing the excitatory applicator proximal to the CNS and the inhibitory applicator distal to the excitatory applicator. The excitatory applicator may, for example, supply illumination in the range of 10-100mW/mm^2 of nominally 450±50nm light to the surface of the nerve bundle to activate cation channels in the cell membrane of the target cells within the Vagus nerve while the inhibitory applicator supplies illumination in the range of 10-100mW/mm^2 of nominally 590±50nm light to activate Cl^- ion pumps in the cell membrane of the target cells to suppress errant descending signals from reaching the PNS.

In an alternate embodiment, the inhibitory probe may be activated prior to the excitatory probe to bias the nerve to suppress errant signals. For example, activating the inhibitory probe at least 5ms prior to the excitatory probe allows time for

the Cl- pumps to have cycled at least once for an opsin such as eNpHR3.0, thus potentially allowing for a more robust errant signal inhibition. Other opsins have different time constants, as described elsewhere herein, and subsequently different pre-excitation activation times.

Alternately, a system may be configured such that only either the inhibitory or excitatory probes and/or applicators are optical probes used to illuminate cells containing light-activatable ion channels that reside within a target tissue while other probe is an electrical probe. In the case of the stimulation applicator being an electrical probe, typical neurostimulation parameters, such as those described in U.S. Pat. Application Nos. 13/707,376 and 13/114,686, which are expressly incorporated herein by reference, may be used. The operation of a stimulation probe, including alternative embodiments of suitable output circuitry for performing the same function of generating stimulation pulses of a prescribed amplitude and width, is described in U.S. Pat. Nos. 6,516,227 and 6,993,384, which are expressly incorporated herein by reference. By way of non-limiting example, parameters for driving an electrical neuroinhibition probe, such as those described in U.S. Pat. Application No. 12/360,680, which is expressly incorporated herein by reference, may be used. When the neuroinhibition is accomplished using an electrical probe, the device may be operated in a mode that is called a "high frequency depolarization block". By way of non-limiting example, for details regarding the parameters for driving a high frequency depolarization block electrical probe reference can be made to Kilgore KL and Bhadra N, *High Frequency Mammalian Nerve Conduction Block: Simulations and Experiments*, Engineering in Medicine and Biology Society, 2006. EMBS '06. 28th Annual

International Conference of the IEEE, pp. 4971 - 4974, which is expressly incorporated herein by reference.

In further embodiments, sensors may be used to ascertain the amount of errant signal suppression in a closed-loop manner to adjust the inhibitory system parameters. An example of such a system is shown in Figure 23 where a sensor SEN is located passed the inhibition probe ascertain the degree of errant nerve signal suppression. Sensor SEN may be configured to measure the nerve signal by using an ENG probe, for example. It can alternately be a therapeutic sensor configured to monitor a physical therapeutic outcome directly, or indirectly. Such a therapeutic sensor may be, by way of non-limiting example, an ENG probe, an EMG probe, a pressure transducer, a chemical sensor, an EKG sensor, or a motion sensor. A direct sensor is considered to be one that monitors a therapeutic outcome directly, such as the aforementioned examples of chemical and pressure sensors. An indirect sensor is one that monitors an effect of the treatment, but not the ultimate result. Such sensors are the aforementioned examples of ENG, EKG, and EMG probes, as has been described elsewhere herein.

Alternately, the therapeutic sensor may be a patient input device that allows the patient to at least somewhat dictate the optical dosage and/or timing. Such a configuration may be utilized, by way of non-limiting example, in cases such as muscle spasticity or cough, where the patient may control the optical dosage and/or timing to provide what they deem to be the requisite level of control for a given situation.

As described herein with regard to probe and/or applicator placement, distal refers to more peripheral placement, and proximal refers to more central placement along a nerve. As such, an inhibition probe that is located distally to an

excitation probe may be used to provide ascending nerve signals while suppressing descending nerve signals. Equivalently, this configuration may be described as an excitation probe that is located proximally to an inhibition probe. Similarly, an excitation probe that is located distally to an inhibition probe may be used to provide descending nerve signals while suppress ascending nerve signals. Equivalently, this configuration may be described as an inhibition probe that is located proximally to an excitation probe. Descending signals travel in the efferent direction away from the CNS towards the PNS, and vice versa ascending signals travel in the afferent direction.

In certain scenarios wherein light sensitivity of opsin genetic material is of paramount importance, it may be desirable to focus less on wavelength (as discussed above, certain "red-shifted" opsins may be advantageous due to the greater permeability of the associated radiation wavelengths through materials such as tissue structures) and more on a tradeoff that has been shown between response time and light sensitivity (or absorption cross-section). In other words, optimal opsin selection in many applications may be a function of system kinetics and light sensitivity. Referring to the plot (252) of Figure 49A, for example, electrophysiology dose for a 50% response (or "EPD50"; lower EPD50 means more light-sensitive) is plotted versus temporal precision ("tau-off", which represents the time constant with which an opsin deactivates after the illumination has been discontinued). This data is from Mattis et al, Nat Methods 2011, Dec 10; 9(2): 159-172, which is incorporated by reference herein in its entirety, and illustrates the aforementioned tradeoff. In addition to EPD50 and tau-off, other important factors playing into opsin selection optimization may include exposure density ("H-thresh")

and photocurrent levels. H-thresh may be assessed by determining the EPD50 dose for an opsin; the longer the channel created by the opsin requires to "reset", the longer the associated membrane will remain polarized, and thus will block further depolarization. The following table features a few exemplary opsins with characteristics compared.

Opsin	EPD50 [mW/mm2]	Tau-off [ms]	Lambda Peak [nm]	Pentration Depth [normalized to 475nm]	Peak Photocurrent [nA]	SS Photocurrent [nA]	Peak Potential [mV]
C1V1t	0.3	75	540	1.67	1.5	1	30
C1V1tt	0.4	50	540	1.67	1.1	0.6	32
CatCh	0.3	60	475	1.00	1.25	1	38
VChR1	0.1	100	550	1.80			

Thus, the combination of low exposure density (H-thresh), long photorecovery time (tau-off), and high photocurrent results in an opsin well-suited for applications that do not require ultra-temporal precision, such as those described herein for addressing satiety, vision restoration, and pain. As described above, a further consideration remains the optical penetration depth of the light or radiation responsible for activating the opsin. Tissue is a turbid medium, and predominantly attenuates the power density of light by Mie (elements of similar size to the wavelength of light) and Rayleigh (elements of smaller size than the wavelength of light) scattering effects. Both effects are inversely proportional to the wavelength, i.e. shorter wavelength is scattered more than a longer wavelength. Thus, a longer opsin excitation wavelength is preferred, but not required, for configurations where there is tissue interposed between the illumination source and the target. A balance may be made between the ultimate irradiance (optical power density

and distribution) at the target tissue containing the opsin and the response of the opsin itself. The penetration depth in tissue (assuming a simple lambda^{-4} scattering dependence) is listed in the table above. Considering all the abovementioned parameters, both C1V1t and VChR1 are desirable choices in many clinical scenarios, due to combination of low exposure threshold, long photorecovery time, and optical penetration depth. Figures 49B-49C and 49E-49I feature further plots (254, 256, 260, 262, 264, 266, 268, respectively) containing data from the aforementioned incorporated Mattis et al reference, demonstrating the interplay/relationships of various parameters of candidate opsins. Figure 49D features a plot (258) similar to that shown in Figure 3B, which contains data from Yizhar et al, Neuron. 2011 July; 72:9-34, which is incorporated by reference herein in its entirety. The table (270) of Figure 49J features data from the aforementioned incorporated Yizhar et al reference, in addition to Wang et al, 2009, Journal of Biological Chemistry, 284: 5625-5696 and Gradinaru et al, 2010, Cell: 141:1-12, both of which are incorporated by reference herein in their entirety.

Excitatory opsins useful in the invention may include red-shifted depolarizing opsins including, by way of non-limiting examples, C1V1 and C1V1 variants C1V1/E162T and C1V1/E122T/E162T; blue depolarizing opsins including ChR2/L132C and ChR2/T159C and combinations of these with the ChETA substitutions E123T and E123A; and SFOs including ChR2/C128T, ChR2/C128A, and ChR2/C128S. These opsins may also be useful for inhibition using a depolarization block strategy. Inhibitory opsins useful in the invention may include, by way of non-limiting examples, NpHR, Arch, eNpHR3.0 and eArch3.0. Opsins including trafficking motifs may be useful. An inhibitory opsin

may be selected from those listed in Figure 49J, by way of non-limiting examples. A stimulatory opsin may be selected from those listed in Figure 49J, by way of non-limiting examples. An opsin may be selected from the group consisting of Opto-β2AR or Opto-α1AR, by way of non-limiting examples. The sequences illustrated in Figures 38A-48Q pertain to opsin proteins, trafficking motifs, and polynucleotides encoding opsin proteins related to configurations described herein. Also included are amino acid variants of the naturally occurring sequences, as determined herein. Preferably, the variants are greater than about 75% homologous to the protein sequence of the selected opsin, more preferably greater than about 80%, even more preferably greater than about 85% and most preferably greater than 90%. In some embodiments the homology will be as high as about 93 to about 95 or about 98%. Homology in this context means sequence similarity or identity, with identity being preferred. This homology will be determined using standard techniques known in the art. The compositions of the present invention include the protein and nucleic acid sequences provided herein including variants which are more than about 50% homologous to the provided sequence, more than about 55% homologous to the provided sequence, more than about 60% homologous to the provided sequence, more than about 65% homologous to the provided sequence, more than about 70% homologous to the provided sequence, more than about 75% homologous to the provided sequence, more than about 80% homologous to the provided sequence, more than about 85% homologous to the provided sequence, more than about 90% homologous to the provided sequence, or more than about 95% homologous to the provided sequence.

In one embodiment, for example, the housing (H) comprises control circuitry and a power supply; the delivery system (DS) comprises an electrical lead to pass power and monitoring signals as the lead operatively couples the housing (H) to the applicator (A); the applicator (A) preferably comprises a single fiber output style applicator, which may be similar to those described elsewhere herein. Generally the opsin configuration will be selected to facilitate controllable inhibitory neuromodulation of the associated neurons within the targeted neuroanatomy in response to light application through the applicator. Thus in one embodiment an inhibitory opsin such as NpHR, eNpHR 3.0, ARCH 3.0, or ArchT, or Mac 3.0 may be utilized. In another embodiment, an inhibitory paradigm may be accomplished by utilizing a stimulatory opsin in a hyper-activation paradigm, as described above. Suitable stimulatory opsins for hyperactivation inhibition may include ChR2, VChR1, certain Step Function Opsins (ChR2 variants, SFO), ChR2/L132C (CatCH), excitatory opsins listed herein, or a red-shifted C1V1 variant (e.g., C1V1) or the Chrimsom family of opsins, which may assist with illumination penetration through fibrous tissues which may tend to creep in or encapsulate the applicator (A) relative to the targeted neuroanatomy. In another embodiment, an SSFO may be utilized. An SFO or an SSFO or an inhibitory channel is differentiated in that it may have a time domain effect for a prolonged period of minutes to hours, which may assist in the downstream therapy in terms of saving battery life (i.e., one light pulse may get a longer-lasting physiological result, resulting in less overall light application through the applicator A). As described above, preferably the associated genetic material is delivered via viral transfection in association with injection paradigm, as described above. An

inhibitory opsin may be selected from those listed in Figure 49J, by way of non-limiting examples. A stimulatory opsin may be selected from those listed in Figure 49J, by way of non-limiting examples. An opsin may be selected from the group consisting of Opto-β2AR or Opto-α1AR, by way of non-limiting examples. Alternately, an inhibitory channel may also be chosen, and either a single blue light source used for activation, or a combination of blue and red light sources to provide for channel activation and deactivation, as has been described elsewhere herein, such as with regard to Figure 14.

Alternately, a system may be configured to utilize one or more wireless power transfer inductors/receivers that are implanted within the body of a patient that are configured to supply power to the implantable power supply.

There are a variety of different modalities of inductive coupling and wireless power transfer. For example, there is non-radiative resonant coupling, such as is available from Witricity, or the more conventional inductive (near-field) coupling seen in many consumer devices. All are considered within the scope of the present invention. The proposed inductive receiver may be implanted into a patient for a long period of time. Thus, the mechanical flexibility of the inductors may need to be similar to that of human skin or tissue. Polyimide that is known to be biocompatible was used for a flexible substrate.

By way of non-limiting example, a planar spiral inductor may be fabricated using flexible printed circuit board (FPCB) technologies into a flexible implantable device. There are many kinds of a planar inductor coils including, but not limited to; hoop, spiral, meander, and closed configurations. In order to concentrate a magnetic flux and field between two inductors, the

permeability of the core material is the most important parameter. As permeability increases, more magnetic flux and field are concentrated between two inductors. Ferrite has high permeability, but is not compatible with microfabrication technologies, such as evaporation and electroplating. However, electrodeposition techniques may be employed for many alloys that have a high permeability. In particular, Ni (81%) and Fe (19%) composition films combine maximum permeability, minimum coercive force, minimum anisotropy field, and maximum mechanical hardness. An exemplary inductor fabricated using such NiFe material may be configured to include 200μm width trace line width, 100μm width trace line space, and have 40 turns, for a resultant self-inductance of about 25μH in a device comprising a flexible 24mm square that may be implanted within the tissue of a patient. The power rate is directly proportional to the self-inductance.

The radio-frequency protection guidelines (RFPG) in many countries such as Japan and the USA recommend the limits of current for contact hazard due to an ungrounded metallic object under the electromagnetic field in the frequency range from 10 kHz to 15 MHz. Power transmission generally requires a carrier frequency no higher than tens of MHz for effective penetration into the subcutaneous tissue.

In certain embodiments of the present invention, an implanted power supply may take the form of, or otherwise incorporate, a rechargeable micro-battery, and/or capacitor, and/or super-capacitor to store sufficient electrical energy to operate the light source and/or other circuitry within or associated with the implant when used along with an external wireless power transfer device. Exemplary microbatteries, such as the Rechargeable NiMH button cells available from VARTA, are

within the scope of the present invention. Supercapacitors are also known as electrochemical capacitors.

An inhibitory opsin protein may be selected from the group consisting of, by way of non-limiting examples: NpHR, eNpHR 1.0, eNpHR 2.0, eNpHR 3.0, Mac, Mac 3.0, Arch, Arch3.0, ArchT, Jaws, iC1C2, iChR, and SwiChR families. An inhibitory opsin may be selected from those listed in Figure 49J, by way of non-limiting examples. A stimulatory opsin protein may be selected from the group consisting of, by way of non-limiting examples: ChR2, C1V1-E122T, C1V1-E162T, C1V1-E122T/E162T, CatCh, CheF, ChieF, Chrimson, VChR1-SFO, and ChR2-SFO. A stimulatory opsin may be selected from those listed in Figure 49J, by way of non-limiting examples. An opsin may be selected from the group consisting of Opto-β2AR or Opto-α1AR, by way of non-limiting examples. The light source may be controlled to deliver a pulse duration between about 0.1 and about 20 milliseconds, a duty cycle between about 0.1 and 100 percent, and a surface irradiance of between about 50 milliwatts per square millimeter to about 2000 milliwatts per square millimeter at the output face of a 100 - 200 um core diameter optical fiber.

Figures 69A and 69B show an alternate embodiment of the present invention, where a Trocar and Cannula may be used to deploy an at least partially implantable system for optogenetic control of at least potions of the basal ganglia. Trocar TROCAR may be used to create a tunnel through tissue between surgical access points that may correspond to the approximate intended deployment locations of elements of the present invention, such as applicators and housings. Cannula CANNULA may be inserted into the tissue of the patient along with, or after the insertion of the trocar. The trocar may be removed following insertion and placement of the cannula to provide an open lumen

for the introduction of system elements. The open lumen of cannula CANNULA may then provide a means to locate delivery segment DS along the route between a housing and an applicator. The ends of delivery segment DS may be covered by end caps ENDC. End caps ENDC may be further configured to comprise radio-opaque markings ROPM to enhance the visibility of the device under fluoroscopic imaging and/or guidance. End Caps ENDC may provide a watertight seal to ensure that the optical surfaces of the Delivery Segment DS, or other system component being implanted, are not degraded. The cannula may be removed subsequent to the implantation of delivery segment DS. Subsequently, delivery segment DS may be connected to an applicator that is disposed to the target tissue and/or a housing, as have been described elsewhere herein. In a further embodiment, the End Caps ENDC, or the Delivery Segment DS itself may be configured to also include a temporary Tissue Fixation elements AFx, such as, but not limited to; hook, tines, and barbs, that allow the implanted device to reside securely in its location while awaiting further manipulation and connection to the remainder of the system.

Figure 70 illustrates an alternate embodiment, similar to that of Figures 69A and 69B, further configured to utilize a barbed Tissue Fixation Element AF that is affixed to End Cap ENDC. Tissue Fixation Element AF may be a barbed, such that it will remain substantially in place after insertion along with Cannula CANNULA, shown in this example as a hypodermic needle with sharp End SHARP being the leading end of the device as it is inserted into a tissue of a patient. The barbed feature(s) of Tissue Fixation Element AF insert into tissue, substantially disallowing Delivery Segment DS to be removed. In a still further embodiment, Tissue Fixation Element AF may be made responsive to an actuator, such as a trigger mechanism (not

shown) such that it is only in the configuration to affirmatively remain substantially in place after insertion when activated, thus providing for the ability to be relocated more easily during the initial implantation, and utilized in conjunction with a forward motion of Delivery Segment DS to free the end from the tissue it has captured. Delivery Segment DS may be substantially inside the hollow central lumen of Cannula CANNULA, or substantially slightly forward of it, as is shown in the illustrative embodiment. As used herein, cannula also refers to an elongate member, or delivery conduit. The elongate delivery conduit may be a cannula. The elongate delivery conduit may be a catheter. The catheter may be a steerable catheter. The steerable catheter may be a robotically steerable catheter, configured to have electromechanical elements induce steering into the elongate delivery conduit in response to commands made by an operator with an electronic master input device that is operatively coupled to the electromechanical elements. The surgical method of implantation further may comprise removing the elongate delivery conduit, leaving the delivery segment in place between the first anatomical location and the second anatomical location.

An alternate embodiment of the invention may comprise the use of a SFO and/or a SSFO opsin in the cells of the target tissue to affect neural inhibition of the targeted vagal afferents, such a system may comprise a 2-color illumination system in order to activate and then subsequently deactivate the light sensitive protein. As is described elsewhere herein, the step function opsins may be activated using blue or green light, such as a nominally 450nm LED or laser light source, and may be deactivated using a yellow or red light, such as a nominally 600nm LED of laser light source. The temporal coordination of

these colors may be made to produce a hyperstimulation (depolarization) block condition by pulsing the first light source for activation to create an activation pulse of a duration between 0.1 and 10ms, then pulsing the second light source for deactivation to create a deactivation pulse of a duration between 0.1 to 10ms at a time between 1 and 100ms after the completion of the activation pulse from the first light source. Alternately, certain inhibitory opsins, such as, but not limited to, NpHR and Arch, may be similarly deactivated using blue light.

It is understood that systems for therapeutic intervention of movement disorders may be configured from combinations of any of the applicators, controllers/housings, delivery segments, and other system elements described, and utilize therapeutic parameters defined herein. By way of non-limiting example, a system comprising a nominally 590nm LED light source may be operatively coupled to a waveguide delivery segment, comprised of a 100μm diameter optical fiber, via a hermetic optical feedthrough to transmit light from within an implantable housing, and controlled by a controller therein, to an applicator, which may be comprised of a single fiber output face, that may be disposed within or about the STN to illuminate cells containing an NpHR opsin within the target tissue with a pulse duration of between 0.1-10ms, a duty cycle of between 20-70%, or constantly, and an irradiance of between 50-2000mW/mm^2 at the output face of the applicator or probe to illuminate a tissue a nominally spherical volume of between approximately 30mm^3 to approximately 70mm^3. That is centered about 500 distal to the fiber output face.

Specifically addressing movement disorders:

Figure 71 illustrates an embodiment of the present inventive therapy wherein atleast a portion of a subthalamic nucleus (STN) of the brain of a patient is illuminated by light field LF1 via an applicator (A) to inhibit the output of nerve cells 2000 that communicate with the substantia nigra (SNr) and possibly nerve cells 2004 that communicate with the Globus pallidus Externa (GPe), both of which may in turn serve to regulate the neural output to the thalamus via nerve cells 2002 and 2006, respectively. A further embodiment is also configured to illuminate light field LF2 within the substantia nigra (SNr) itself. In this schematic description of brain neural circuitry, nerve cells 2008 communicate with from the globus pallidus interna (GPi) to the GPe, and nerve cells 2010 within the GPe communicate with the STN.

Referring to Figure 72A, an embodiment is illustrated wherein after creating surgical access to a targeted tissue structure, such as the subthalamic nucleus neuroanatomy of the central nervous system of a human (2100), an effective amount of polynucleotide encoding a light-responsive opsin protein which is to be expressed in neurons of the targeted neuroanatomy is delivered (2102). A period of waiting time may be consumed to ensure that sufficient portions of the targeted neuroanatomy will express the light-responsive opsin protein driven currents upon exposure to light (2104), after which an optical applicator may be placed within or adjacent to targeted neuroanatomy to provide light access to the targeted neuroanatomy through the applicator (2106). With the applicator in place, light may be delivered to the targeted neuroanatomy to cause controlled functional modulation for therapeutic use (2108).

Referring to Figure 72B, in an embodiment with some similarities to that of Figure 72A but with a different order of

events, after creating surgical access (2100), an applicator may be positioned and/or implanted within or adjacent to targeted neuroanatomy (2106) before the delivery of the effective amount of polynucleotide encoding a light-responsive opsin protein which is to be expressed in neurons of the targeted neuroanatomy (2102). Thereafter, a period of waiting time may be consumed to ensure that sufficient portions of the targeted neuroanatomy will express the light-responsive opsin protein driven currents upon exposure to light (2104), and light may be delivered to the targeted neuroanatomy to cause controlled functional modulation for therapeutic use (2108).

Referring to Figure 72C, in an embodiment with some similarities to that of Figure 72A or Figure 72B but with a different order of events, after creating surgical access (2100), an applicator may be positioned and/or implanted within or adjacent to targeted neuroanatomy (2106) at the same or approximately same time as the delivery of the effective amount of polynucleotide encoding a light-responsive opsin protein which is to be expressed in neurons of the targeted neuroanatomy (2102). Thereafter, a period of waiting time may be consumed to ensure that sufficient portions of the targeted neuroanatomy will express the light-responsive opsin protein driven currents upon exposure to light (2104), and light may be delivered to the targeted neuroanatomy to cause controlled functional modulation for therapeutic use (2108).

Figures 73-75 illustrate embodiments wherein additional neuroanatomy is involved with order of events configurations similar to those illustrated in Figure 72A; it is important to note that orders of events for each of these configurations (Figures 73-75) also may be conducted in parallel to the orders

to be optical fibers, such as 105µm core diameter/125µm cladding diameter/225µm acrylate coated 0.22NA step index fiber that is enclosed in a protective sheath, such as a 300µm OD silicone or PEEK tube whose distal end may be encapsulated with a biocompatible material, such as but not limited to epoxy, to minimize contact between the optical fiber and fluids within the body. Connectors C1 & C2 are configured to operatively couple light from Delivery Segments DS1 & DS2 to Applicators A1 & A2, respectively. Delivery Segments DS1 & DS2 further comprise Undulations U1 & U2, respectively, which may provide strain relief. Delivery Segments DS1 & DS2 are operatively coupled to Housing H via Optical Feedthroughs OFT1 & OFT2, respectively. Light is provided to Delivery Segments DS1 & DS2 from Light Sources LS1 & LS2, respectively, within Housing H. Light Sources LS1 & LS2 may be configured to be LEDs, and/or lasers that provide spectrally different output to activate and/or deactivate the opsins resident within target tissue(s), as dictated by the therapeutic paradigm. For example, LS1 may be configured to be a blue laser source, such as the NDA4116 from Nichia that produces up to 120mW of 473nm light with a slope efficiency of ~1W/A, or the NDB4216E from Nichia that produces up to 120mW of 450nm light with a slope efficiency of ~1.5W/A, which are suitable for use in optogenetic intervention using such opsins as ChR2, iC1C2, and/or iChR2, by way of non-limiting example. Light Source LS2 may be configured to be a different laser than LS1, such as the QLD0593-9420 from QD Photonics that produces up to 50 mW of 589 nm light and is suitable for use in optogenetic inhibition using NpHR.

In an alternate embodiment, an inhibitory opsin such as Arch or Arch-T may be expressed with the STN, and an excitatory opsin, such as Chrimson may be made to express within neurons

the substantia nigra pars reticulate (SNr) and globus pallidus interna (GPi). In Parkinson's disease, abnormal STN firing drives abnormal firing of the SNr and GPi, which leads to abnormal outflow of information to the thalamus and the rest of the brain areas controlling movement. In this embodiment, inhibition of STN firing using a hyperpolarizing opsin in response to the correct wavelength of light leads to reduction in the abnormal drive of the GPi and SNr, leading to improved motor function. This generally does not influence nearby axons outside of the STN or adversely influence functions served by those axons, such as speech and swallowing or sensation. The light delivered may be continuous or may be pulsatile at an optimized rate and longevity of light pulse delivery.

In addition to light delivery to the STN, light also may be delivered to the SNr. This may be achieved by a single light probe, which, in one embodiment, may be readily placed through the STN and into the SNr in a single trajectory. Light delivery to the SNr may then be utilized to inhibit only the firing of the axon terminal coming in from the STN since they harbor the inhibitory opsin and will then allow hyperpolarization of the incoming STN neuron. The light generally does not influence cells intrinsic to the SNr, since the opsin making neurons responsive to light would have been delivered to the STN and only those terminals coming into the SNr would be responsive. This avoids the complications which occur from non-specific electrical stimulation of this brain region, which are due to stimulation of nearby unrelated axonal connections and intrinsic neurons within the SNr. This also permits focal capture of the STN neuronal terminals where they are most functional, and inhibits the collateral connections of these neurons to the GPi as well. This is depicted as neuron "1" in Figure 1, with the

example using the iChR responding to blue light to inhibit firing of the axonal terminals in the SNr. Also in Figure 1, inhibition of the cell bodies within the STN is similarly depicted using blue light to activate the inhibitory iChR channel, in this example. Other inhibitory channels or pumps responding to appropriate wavelengths of light may be similarly utilized for this purpose.

In another embodiment, additional portions of the circuit may be engaged to more completely restore functioning of the broader basal ganglia circuit regulating movment and thereby further improve functional (i.e. therapeutic) efficacy. In such case, opsins to activate neurons may be delivered via gene therapy to neurons of the globus pallidus externa (GPe). In Parkinson's disease, GPe neuronal activity is reduced, leading to the abnormal increase in STN activity. In addition, the same neurons projecting to the STN also send collateral connections to the GPi. Therefore, the reduced activity of the GPe neurons in Parkinson's disease not only lead to pathologically increased STN activity, but also worsen the pathologically increase GPi activity. Following opsin delivery to the GPe, the light probe is again inserted into the STN as described above. The neuronal terminals coming into the STN from the GPe are then activated by the appropriate wavelength of light, such as blue light to activate neurons when ChR is delivered as the excitatory opsin. Activating these GPe neurons normalize their activity, and in turn further normalize STN activity, either alone or in combination with the example described above. Since these neurons also send collaterals to the GPi, activating their terminals within the STN also lead to firing of the entire neuron, including the collateral connections to the GPi.

Therefore, this also improves GPe signaling to the GPi, thereby further normalizing GPi activity. Thus, in this example, a single light probe going through the STN to the SNr, along with opsin gene delivery to the STN and the GPe may be utilized to normalize most of the basal ganglia circuitry in Parkinson's disease.

This example is also depicted in Figure 1 as neuron "2" within the GPe. In this example, ChR is delivered to the GPe in order to permit activation by blue light. The combination of ChR in the GPe and iChR in the STN then permits simultaneous inhibition of STN firing and activation of GPe firing with the same blue-light pulse delivered to the STN. In an alternative configuration, ChR may be delivered to the GPe to allow activation by blue light, and Arch or NpHR are delivered to the STN to allow inhibition of these neurons by a different light wavelength, so that a multi-channel light device could independently control these two different neuronal populations from the same light device within the STN.

In addition to these configurations, other components of the basal ganglia circuitry may be specifically controlled to improve symptoms of Parkinson's disease. This includes the striatum, which receives dopamine inputs that are eventually lost in the disease. These neurons may be controlled independently by placing opsins with cell-type specific promoter or viral vectors which only deliver gene to specific cell types. In one embodiment, iChR may be delivered to striatal neurons expressing the D2 dopamine receptors to inhibit those cells in response to light, while ChR is delivered to neurons containing D1 receptors in the striatum in order to activate them in

response to light. In such a configuration, blue light simultaneously activates D1 neurons and inhibits D2 neurons, which is the same effect that dopamine has on these neurons. Therefore, a single blue light pulse mimics dopamine release and therefore permits restoration of dopaminergic tone in this region. In another embodiment, D1 and D2 neurons may be independently controlled to activate or inhibit in response to different wavelengths of light delivered from one or more light devices placed in the striatum, in order to tailor optogenetic therapy to particular symptoms at particular time points. In another embodiment, circuit specificity may be achieved by gene delivery to striatal neurons non-specifically, then light devices may be inserted into specific striatal targets, including GPi and GPe, to independently or simultaneously control striatal output to these structures. In another example is gene delivery of opsins to cortical neurons which project to STN and to other basal ganglia circuits.

Referring again to Figure 1, an opsin gene (inhibitory channelrhodopsin; iChR) is delivered to neuron "1" within the subthalamic nucleus (STN). Neuron 1 from the STN projects to the substantia nigra reticulate (SNr) and globus pallidus interna (GPi), both of which represent the major outflow structures to the rest of the brain from the basal ganglia circuit which controls movement. Blue-light delivery to the STN inhibits firing of the STN neurons. Blue-light delivery to the SNr specifically inhibits those STN neurons which project to the SNr.

An opsin gene (channelrhodopsin; ChR) is also delivered to neuron 2 of the globus pallidus externa (GPe). Neuron 2

projects to neuron 1 of the STN and releases GABA to inhibit and normalize firing of the STN; neuron 2 also has collateral projections to the GPi and perform the same function. Blue light delivered to the STN activates terminals coming into the STN from GPe neuron 2, thereby normalizing the activity of this neuron and in turn further normalizing the activity of STN neuron 1. This also permits backfiring of neuron 2 to activate the collateral axon to the GPi, thereby normalizing GPe activity to the GPi and thus further normalizing GPi activity. The result is a more complete normalization of GPe, STN, SNr and GPi activity than is achievable with traditional therapeutic means, without influencing unintended neuronal targets, in order to improve therapeutic efficacy and reduce adverse effects.

Figure 79 illustrates results from an animal study involving mice with AAV-mediated transfer of Arch into the STN driven by the CamKII promoter improves spontaneous rotations in the mouse 6OHDA parkinson's disease model in a dose-dependent manner. Several weeks following unilateral chemical lesioning of substantia nigra dopamine neurons, mice develop spontaneous rotational behaviors in the ipsilateral direction to the lesion, due to the imbalance in motor control between the normal and lesioned hemispheres. AAV-CamKII-Arch was then infused into the STN of lesioned mice and 6 weeks later a light probe was inserted into the STN. CamKII is expressed in glutamatergic neurons, which are the primary projection neuron from the STN which is abnormally active in PD, so Arch expression was restricted to STN neurons which are abnormally active in PD. At baseline, animals show an abnormal net ipsilateral rotational behavior. Increasing light intensity led to a dose-dependent reduction in net rotations, with zero net rotations equivalent to normal, unlesioned animals, with higher light doses then

resulting in net contralateral rotations. Control animals expressing the YFP marker gene in place of Arch showed no light-dependent change in rotations.

Figure 80 illustrates results from an animal study involving mice with AAV-mediated transfer of Arch into the STN driven by the CamKII promoter improves overall locomotor activity in the mouse 6OHDA Parkinson's Disease model in a dose-dependent manner. Parkinsonian animals from Figure 80 also demonstrated a light-dose dependent improvement in spontaneous locomotor behavior following optogenetic therapy. Control animals expressing the YFP marker gene in place of Arch showed no light-dependent change in locomotor activity.

Figure 81 illustrates results from an animal study involving mice with AAV-mediated transfer of Arch into the STN driven by the Synapsin promoter improves spontaneous rotations in the mouse 6OHDA Parkinson's Disease model in a dose-dependent manner. Animals were generated as described for Figure 79, but using AAV-Syn-Arch. Synapsin is a pan-neuronal marker expressed in all neurons, so the promoter drives Arch expression in any neuron within the infusion field. Control animals expressing the YFP marker gene in place of Arch showed no light-dependent change in rotations.

Figure 82 illustrates results from an animal study involving mice with AAV-mediated transfer of Arch into the STN driven by the Synapsin promoter improves spontaneous locomotor activity in the mouse 6OHDA parkinson's disease model in a dose-dependent manner. Parkinsonian animals from figure 81 also demonstrated a light-dose dependent improvement in spontaneous locomotor behavior following optogenetic therapy. Control animals expressing the YFP marker gene in place of Arch showed no light-dependent change in locomotor activity.

Figure 83 illustrates results from an animal study involving mice with AAV-mediated transfer of NpHR into the STN driven by the Synapsin promoter improves spontaneous rotations in the mouse 6OHDA Parkinson's Disease model in a dose-dependent manner. Parkinsonism was generated as in Figure 79, but using AAV-Syn-NpHR. Control animals expressing the YFP marker gene in place of NpHR showed no light-dependent change in rotations.

Figure 84 illustrates results from an animal study involving mice with AAV-mediated transfer of NpHR into the STN driven by the Synapsin promoter improves spontaneous locomotor activity in the mouse 6OHDA parkinson's disease model in a dose-dependent manner. Parkinsonian animals from Figure 83 also demonstrated a light-dose dependent improvement in spontaneous locomotor behavior following optogenetic therapy. Control animals expressing the YFP marker gene in place of Arch showed no light-dependent change in locomotor activity.

Various exemplary embodiments of the invention are described herein. Reference is made to these examples in a non-limiting sense. They are provided to illustrate more broadly applicable aspects of the invention. Various changes may be made to the invention described and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process act(s) or step(s) to the objective(s), spirit or scope of the present invention. Further, as will be appreciated by those with skill in the art that each of the individual variations described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the

present inventions. All such modifications are intended to be within the scope of claims associated with this disclosure.

Any of the devices described for carrying out the subject diagnostic or interventional procedures may be provided in packaged combination for use in executing such interventions. These supply "kits" may further include instructions for use and be packaged in sterile trays or containers as commonly employed for such purposes.

The invention includes methods that may be performed using the subject devices. The methods may comprise the act of providing such a suitable device. Such provision may be performed by the end user. In other words, the "providing" act merely requires the end user obtain, access, approach, position, set-up, activate, power-up or otherwise act to provide the requisite device in the subject method. Methods recited herein may be carried out in any order of the recited events which is logically possible, as well as in the recited order of events.

Exemplary aspects of the invention, together with details regarding material selection and manufacture have been set forth above. As for other details of the present invention, these may be appreciated in connection with the above-referenced patents and publications as well as generally known or appreciated by those with skill in the art. The same may hold true with respect to method-based aspects of the invention in terms of additional acts as commonly or logically employed.

In addition, though the invention has been described in reference to several examples optionally incorporating various

features, the invention is not to be limited to that which is described or indicated as contemplated with respect to each variation of the invention. Various changes may be made to the invention described and equivalents (whether recited herein or not included for the sake of some brevity) may be substituted without departing from the true spirit and scope of the invention. In addition, where a range of values is provided, it is understood that every intervening value, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the invention.

Also, it is contemplated that any optional feature of the inventive variations described may be set forth and claimed independently, or in combination with any one or more of the features described herein. Reference to a singular item, includes the possibility that there are plural of the same items present. More specifically, as used herein and in claims associated hereto, the singular forms "a," "an," "said," and "the" include plural referents unless the specifically stated otherwise. In other words, use of the articles allow for "at least one" of the subject item in the description above as well as claims associated with this disclosure. It is further noted that such claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely," "only" and the like in connection with the recitation of claim elements, or use of a "negative" limitation.

Without the use of such exclusive terminology, the term "comprising" in claims associated with this disclosure shall

allow for the inclusion of any additional element--irrespective of whether a given number of elements are enumerated in such claims, or the addition of a feature could be regarded as transforming the nature of an element set forth in such claims. Except as specifically defined herein, all technical and scientific terms used herein are to be given as broad a commonly understood meaning as possible while maintaining claim validity.

The breadth of the present invention is not to be limited to the examples provided and/or the subject specification, but rather only by the scope of claim language associated with this disclosure.

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 137

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 137

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

CLAIMS:

What is claimed:

1. A system for controllably managing motor function in the central nervous system of a patient having a targeted tissue structure that has been genetically modified to have light sensitive protein, comprising:

a. a light delivery element configured to direct radiation to at least a portion of a targeted tissue structure;

b. a light source configured to provide light to the light delivery element; and

c. a controller operatively coupled to light source;

wherein the targeted tissue structure is a portion of the basal ganglia of the patient; and wherein the controller is configured to be automatically operated to illuminate the targeted tissue structure with radiation such that a membrane potential of cells comprising the targeted tissue structure is modulated at least in part due to exposure of the light sensitive protein to the radiation.

2. The system of claim 1, wherein the portion of the basal ganglia of the patient is selected from the group consisting of: a subthalamic nucleus, a substantia nigra, a globus pallidus, a nucleus accumbens, and a putamen.

3. The system of claim 1, wherein an applicator is disposed to illuminate the target tissue structure, the applicator being comprised of at least a light delivery element and a sensor, wherein the sensor is configured to:

a. produce an electrical signal representative of the state of the target tissue or its environment; and

b. deliver the signal to the controller, wherein the controller is further configured to interpret the signal from the sensor and adjust at least one light source output parameter such that the signal is maintained within a desired range, wherein the light source output parameter may be chosen from the group containing of; current, voltage, optical power, irradiance, pulse duration, pulse interval time, pulse repetition frequency, and duty cycle.

4. The system of claim 3, wherein the sensor is selected from the group consisting of: an optical sensor, a temperature sensor, a chemical sensor, and an electrical sensor.

5. The system of claim 1, wherein the controller is further configured to drive the light source in a pulsatile fashion.

6. The system of claim 5, wherein the current pulses are of a duration within the range of 1 millisecond to 100 seconds.

7. The system of claim 5, wherein the duty cycle of the current pulses is within the range of 99% to 0.1%

8. The system of claim 1, wherein the controller is responsive to a patient input.

9. The system of claim 8, wherein the patient input triggers the delivery of current.

10. The system of claim 5, wherein the current controller is further configured to control one or more variables selected from the group consisting of: the current amplitude, the pulse duration, the duty cycle, and the overall energy delivered.

11. The system of claim 1, wherein the light delivery element is placed about at least 60% of circumference of a nerve or nerve bundle.

12. The system of claim 1, wherein the light sensitive protein is an opsin protein.

13. The system of claim 12, wherein the opsin protein is selected from the group consisting of: a depolarizing opsin, a hyperpolarizing opsin, a stimulatory opsin, an inhibitory opsin, a chimeric opsin, and a step-function opsin.

14. The system of claim 12, wherein the opsin protein is selected from the group consisting of: NpHR, eNpHR 1.0, eNpHR 2.0, eNpHR 3.0, SwiChR, SwiChR 2.0, SwiChR 3.0, Mac, Mac 3.0, Arch, ArchT, Arch 3.0, ArchT 3.0, iChR, ChR2, C1V1-T, C1V1-TT, Chronos, Chrimson, ChrimsonR, CatCh, VChR1-SFO, ChR2-SFO, ChR2-SSFO, ChEF, ChIEF, Jaws, ChloC, Slow ChloC, iC1C2, iC1C2 2.0, and iC1C2 3.0.

15. The system of claim 1, wherein the light sensitive protein is delivered to the target tissue using a virus.

16. The system of claim 15, wherein the virus is selected from the group consisting of: AAV1, AAV2, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, lentivirus, and HSV.

17. The system of claim 15, wherein the virus contains a polynucleotide that encodes for the opsin protein.

18. The system of claim 17, wherein the polynucleotide encodes for a transcription promoter.

19. The system of claim 18, wherein the transcription promoter is selected from the group consisting of: CaMKIIa, hSyn, CMV, Hb9Hb, Thy1, and Ef1a.

20. The system of Claim 19, wherein the viral construct is selected from the group consisting of; AAV1-hSyn-Arch3.0, AAV5-CamKII-Arch3.0, AAV1-hSyn-iC1C23.0, AAV5-CamKII- iC1C23.0, AAV1-hSyn-SwiChR3.0, and AAV5-CamKII-SwiChR3.0.

21. The system of Claim 1, wherein the light source emits light having a wavelength that is within a wavelength range that is selected from the group consisting of: 440nm to 490nm, 491nm to 540nm, 541nm to 600nm, 601nm to 650nm, and 651nm to 700nm.

22. The system of Claim 1, wherein the light delivery element comprises an optical fiber.

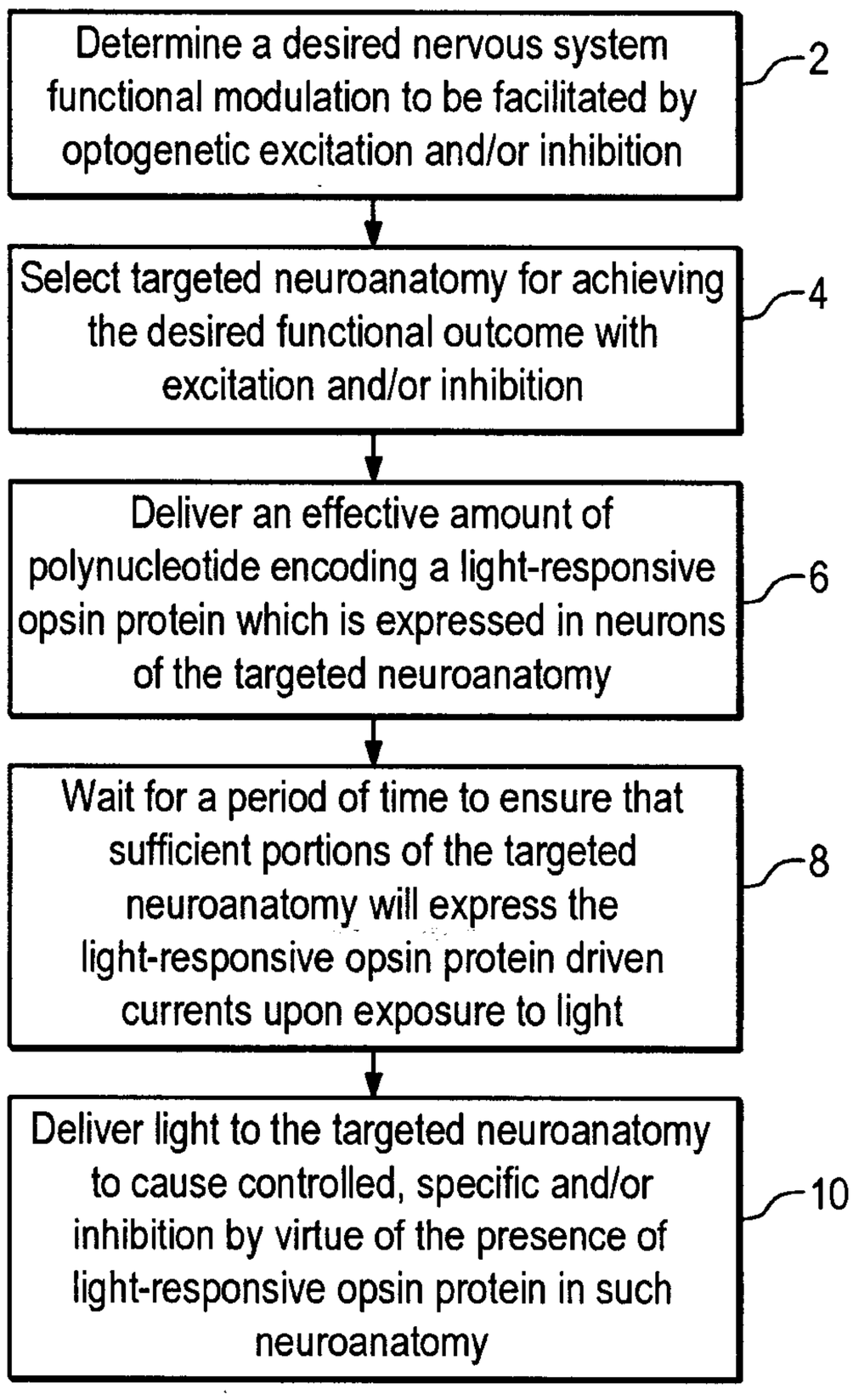
Determine a desired nervous system functional modulation to be facilitated by optogenetic excitation and/or inhibition
2
Select targeted neuroanatomy for achieving the desired functional outcome with excitation and/or inhibition
4
Deliver an effective amount of polynucleotide encoding a light-responsive opsin protein which is expressed in neurons of the targeted neuroanatomy
6
Wait for a period of time to ensure that sufficient portions of the targeted neuroanatomy will express the light-responsive opsin protein driven currents upon exposure to light
8
Deliver light to the targeted neuroanatomy to cause controlled, specific and/or inhibition by virtue of the presence of light-responsive opsin protein in such neuroanatomy
10

FIG. 1

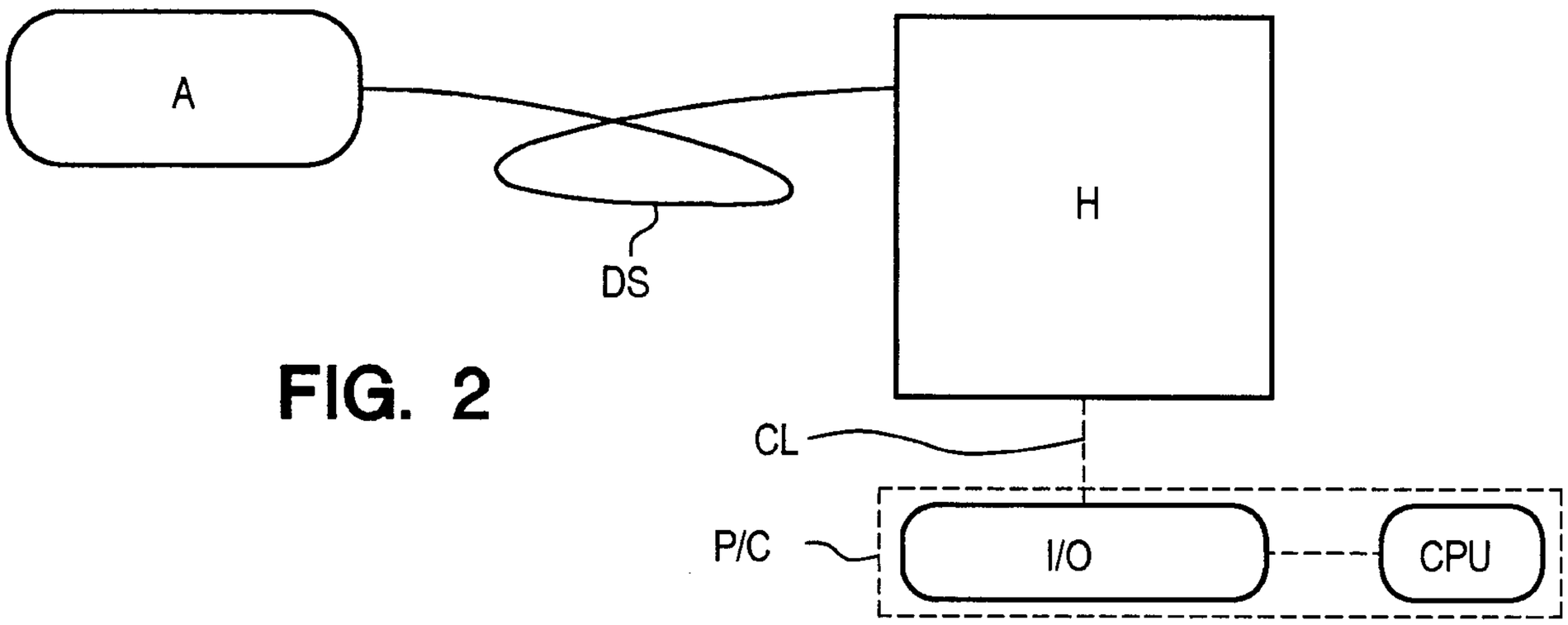
A
DS
H
CL
P/C
I/O
CPU

FIG. 2

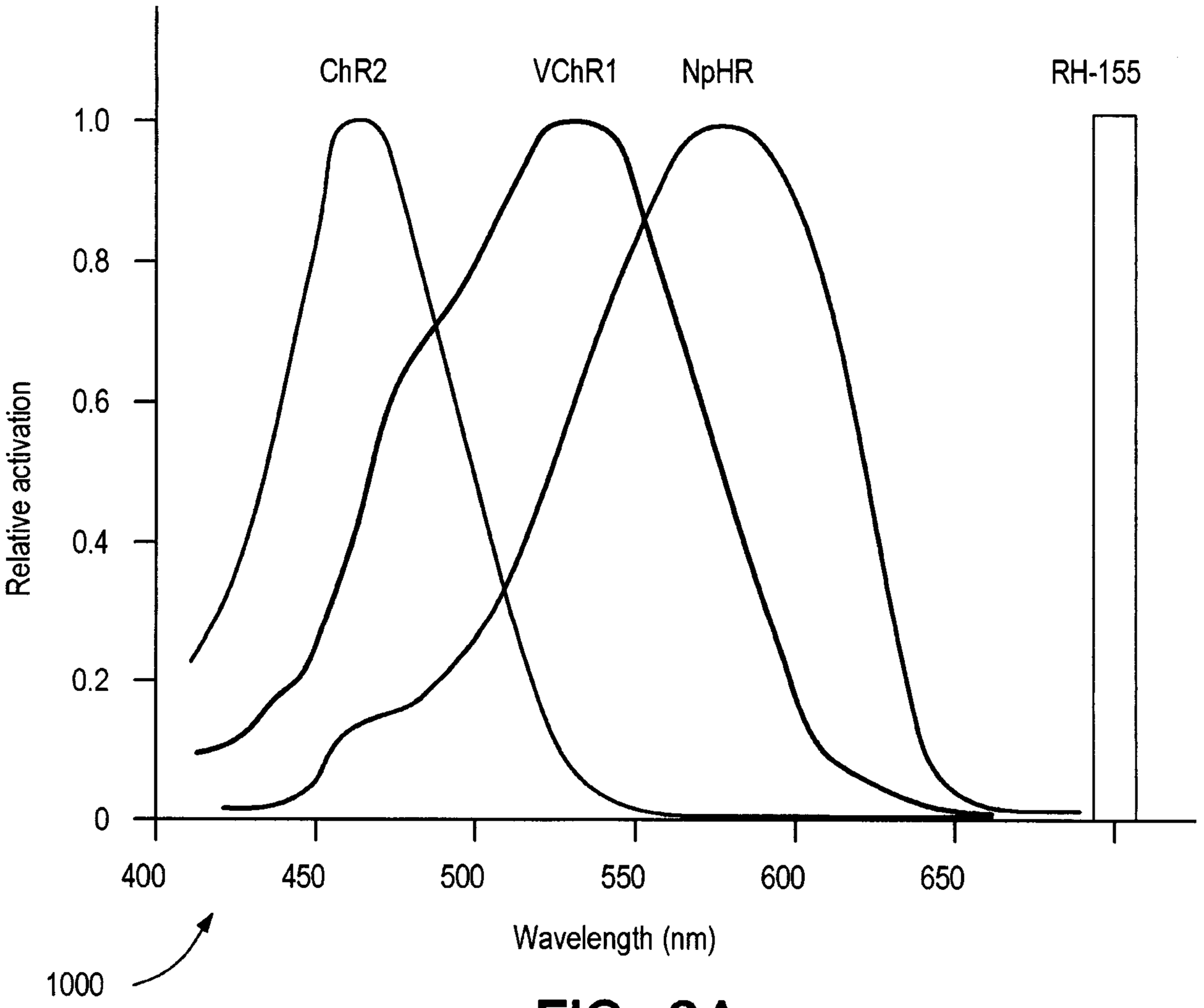
ChR2
VChR1
NpHR
RH-155
1.0
0.8
0.6
0.4
0.2
0
Relative activation
400
450
500
550
600
650
Wavelength (nm)
1000

FIG. 3A

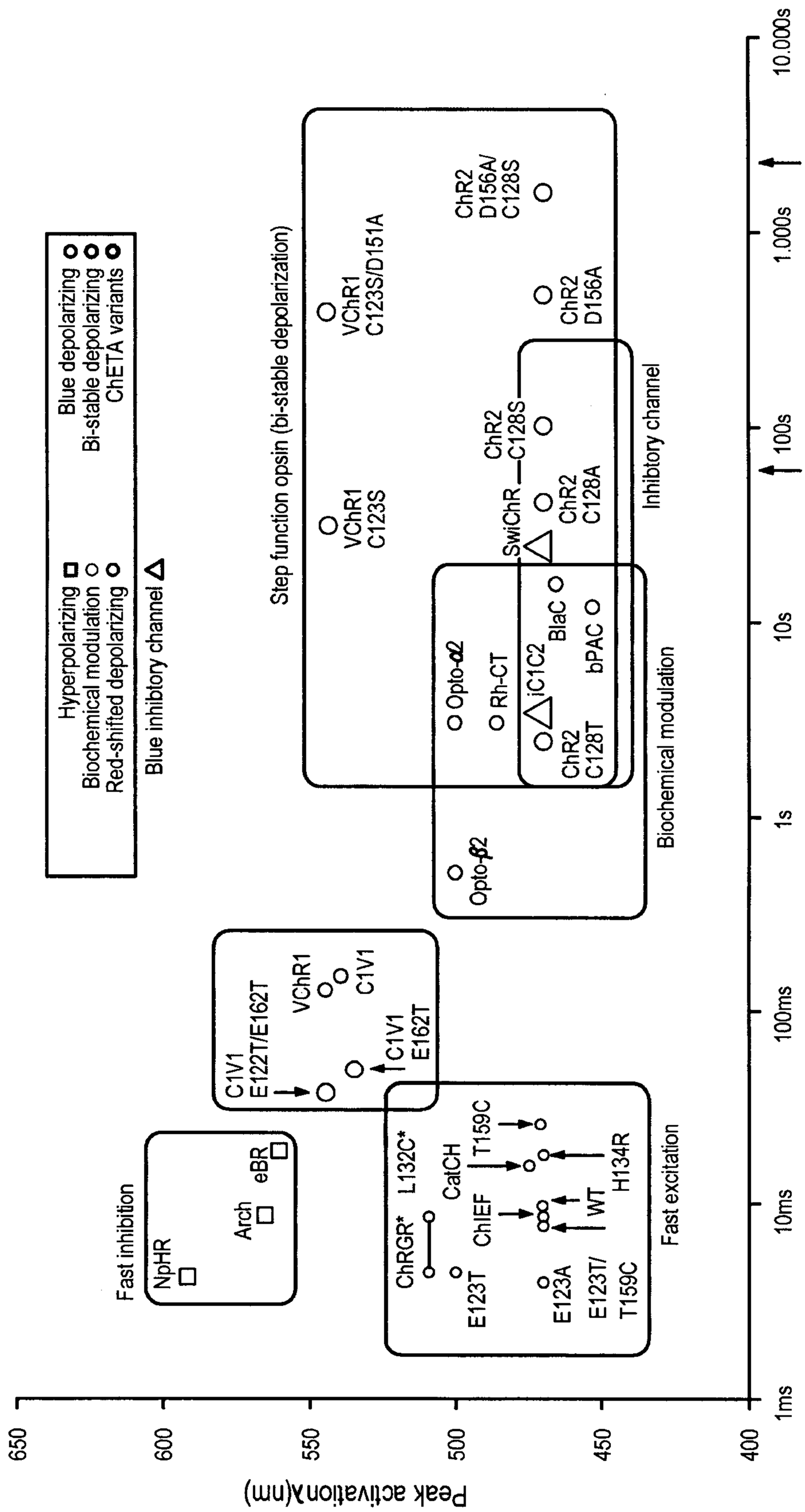
Hyperpolarizing
Biochemical modulation
Red-shifted depolarizing
Blue inhibtory channel
Blue depolarizing
Bi-stable depolarizing
ChETA variants
Step function opsin (bi-stable depolarization)
VChR1 C123S
VChR1 C123S/D151A
ChR2 D156A/ C128S
ChR2 SwiChR—C128S
ChR2 C128A
ChR2 D156A
Inhibtory channel
Opto-α2
Rh-CT
iC1C2
ChR2 C128T
BlaC
bPAC
Opto-β2
Biochemical modulation
C1V1 E122T/E162T
VChR1
C1V1
C1V1 E162T
Fast inhibition
NpHR
Arch
eBR
ChRGR* L132C*
CatCH
T159C
E123T
ChIEF
E123A
E123T/ T159C
WT
H134R
Fast excitation
Peak activation λ(nm)
650
600
550
500
450
400
1ms
100ms
10ms
1s
100s
1min
10s
1.000s
10.000s
30min
τoff
1002

FIG. 3B

	Wavelength (nm)	Color Name	Fwd Voltage (Vf@20ma)	Imtensity 5mm LEDs	Viewing Angle	LED dye Material
	940	Infrared	1.5	16mW @50mA	15°	GaAlAs/GaAs--Gallium Aluminum Arsenide/Gallium Arsenide
	880	Infrared	1.7	18mW @50mA	15°	GaAlAs/GaAs--Gallium Aluminum Arsenide/Gallium Arsenide
	850	Infrared	1.7	26mW @50mA	15°	GaAlAs/GaAs--Gallium Aluminum Arsenide/Gallium Arsenide
	660	Ultra Red	1.8	2000mcd @50mA	15°	GaAlAs/GaAs--Gallium Aluminum Arsenide/Gallium Arsenide
	635	High Eff. Red	2.0	200mcd @20mA	15°	GaAsP/GaP-Gallium Arsenide Phosphide/ Gallium Phosphide
	633	Super Red	2.2	3500mcd @20mA	15°	InGaAlP-Indium Gallium Aluminum Phosphide
	620	Super Orange	2.2	4500mcd @20mA	15°	InGaAlP-Indium Gallium Aluminum Phosphide
	612	Super Orange	2.2	6500mcd @20mA	15°	InGaAlP-Indium Gallium Aluminum Phosphide
	605	Orange	2.1	160mcd @20mA	15°	GaAsP/GaP-Gallium Arsenic Phosphide/ Gallium Phosphide
	595	Super Yellow	2.2	5500mcd @20mA	15°	InGaAlP-Indium Gallium Aluminum Phosphide
	592	Super Pure Yellow	2.1	7000mcd @20mA	15°	InGaAlP-Indium Gallium Aluminum Phosphide

FIG. 3C

	585	Yellow	2.1	100mcd @20mA	15°	GaAsP/GaP-Gallium Arsenic Phosphide/ Gallium Phosphide
	4500K	"Incan-descent" White	3.6	2000mcd @20mA	20°	SiC/GaN--Silicon Carbide/Gallium Nitride
	6500K	Pale White	3.6	4000mcd @20mA	20°	SiC/GaN--Silicon Carbide/Gallium Nitride
	8000K	Cool White	3.6	6000mcd @20mA	20°	SiC/GaN--Silicon Carbide/Gallium Nitride
	574	Super Lime Yellow	2.4	1000mcd @20mA	15°	InGaAlP-Indium Gallium Aluminum Phosphide
	570	Super Lime Green	2.0	1000mcd @20mA	15°	InGaAlP-Indium Gallium Aluminum Phosphide
	565	High Efficiency Green	2.1	200mcd @20mA	15°	GaP/GaP-Gallium Phosphide/Gallium Phosphide
	560	Super Pure Green	2.1	350mcd @20mA	15°	InGaAlP-Indium Gallium Aluminum Phosphide
	555	Pure Green	2.1	80mcd @20mA	15°	GaP/GaP-Gallium Phosphide/Gallium Phosphide
	525	Aqua Green	3.5	10,000mcd @20mA	15°	SiC/GaN--Silicon Carbide/Gallium Nitride
	505	Blue Green	3.5	2000mcd @20mA	45°	SiC/GaN--Silicon Carbide/Gallium Nitride
	470	Super Blue	3.6	3000mcd @20mA	15°	SiC/GaN--Silicon Carbide/Gallium Nitride
	430	Ultra Blue	3.8	100mcd @20mA	15°	SiC/GaN--Silicon Carbide/Gallium Nitride

1004

FIG. 3C CONTINUED

FIG. 3C-1

FIG. 3C-2

FIG. 3C

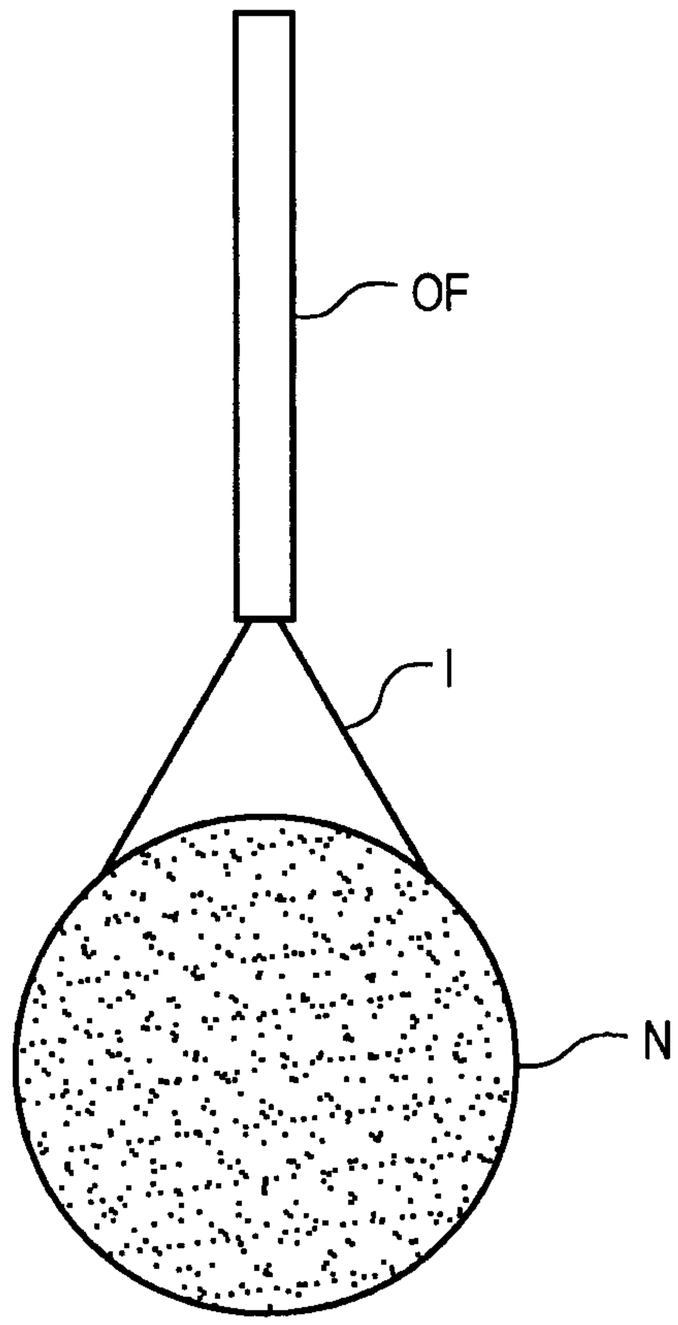

FIG. 4

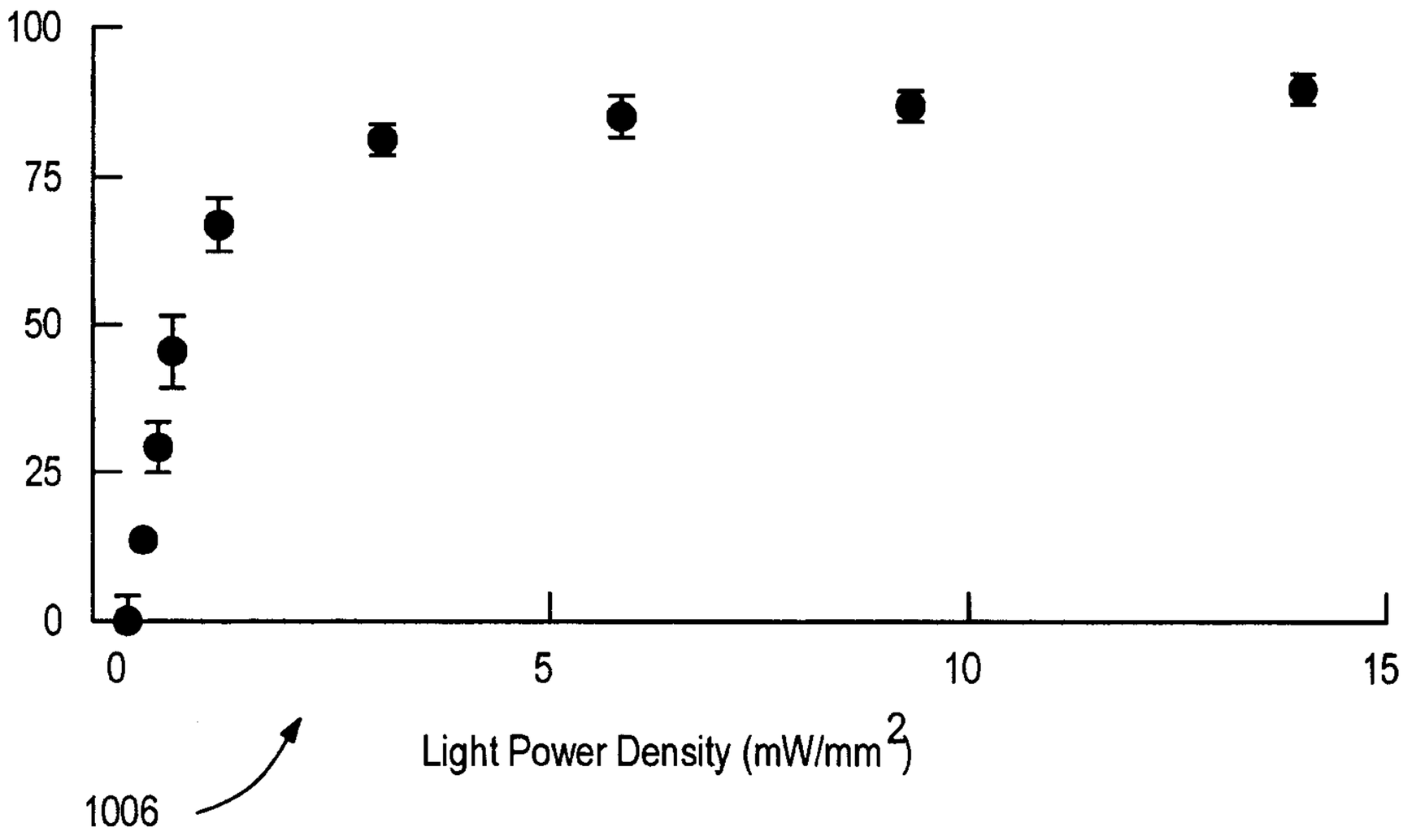

FIG. 5

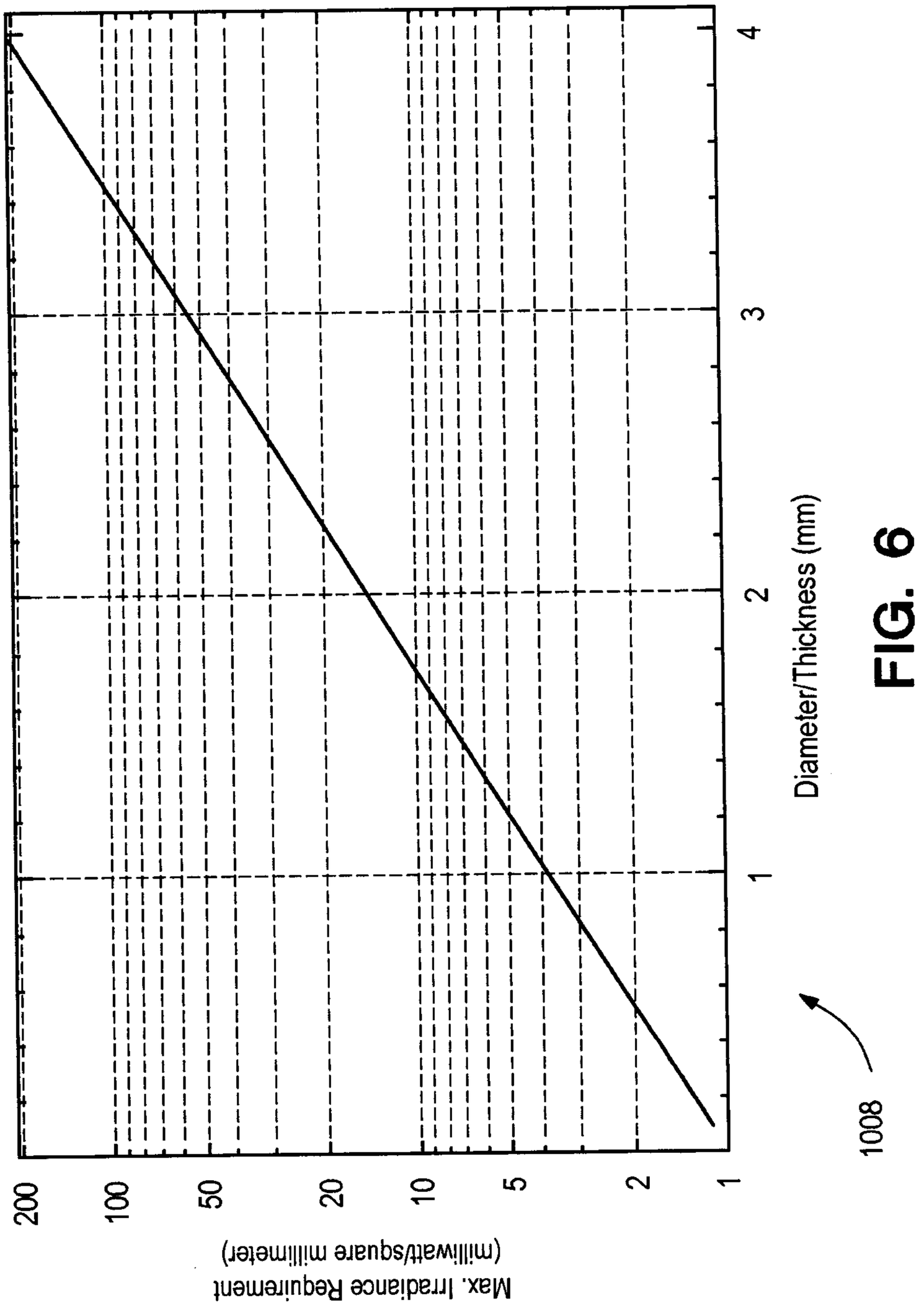
Max. Irradiance Requirement
(milliwatt/square millimeter)
200
100
50
20
10
5
2
1
1008
Diameter/Thickness (mm)
1
2
3
4

FIG. 6

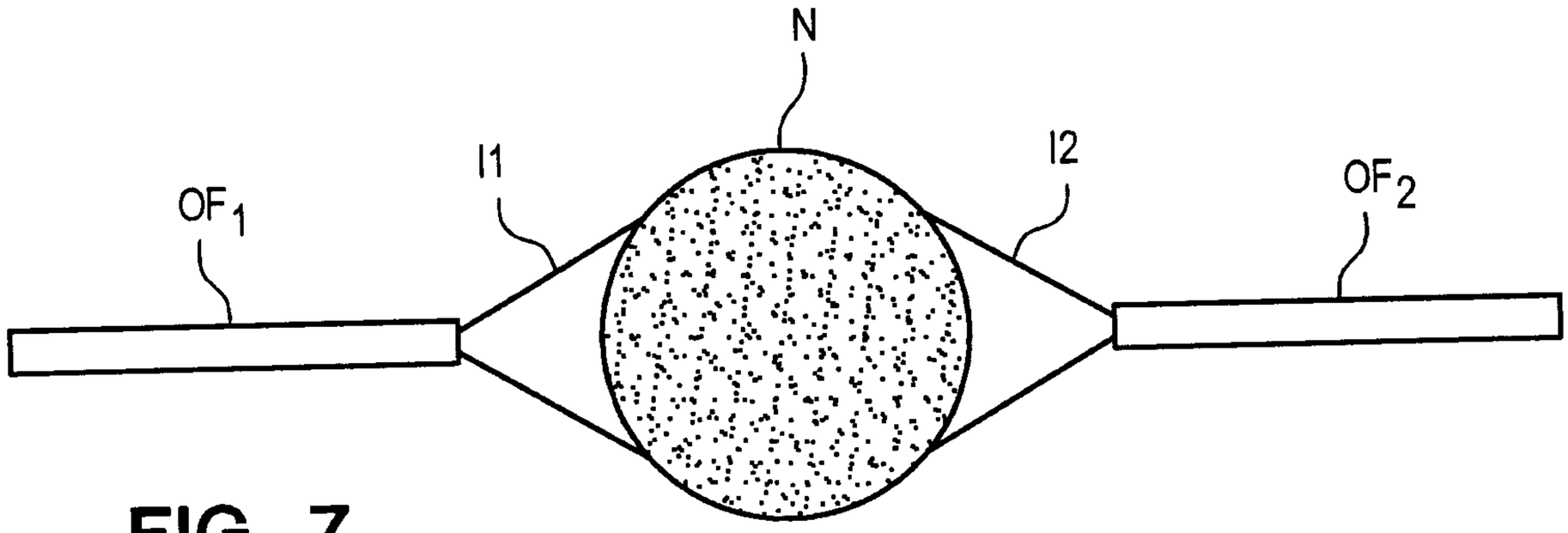

FIG. 7

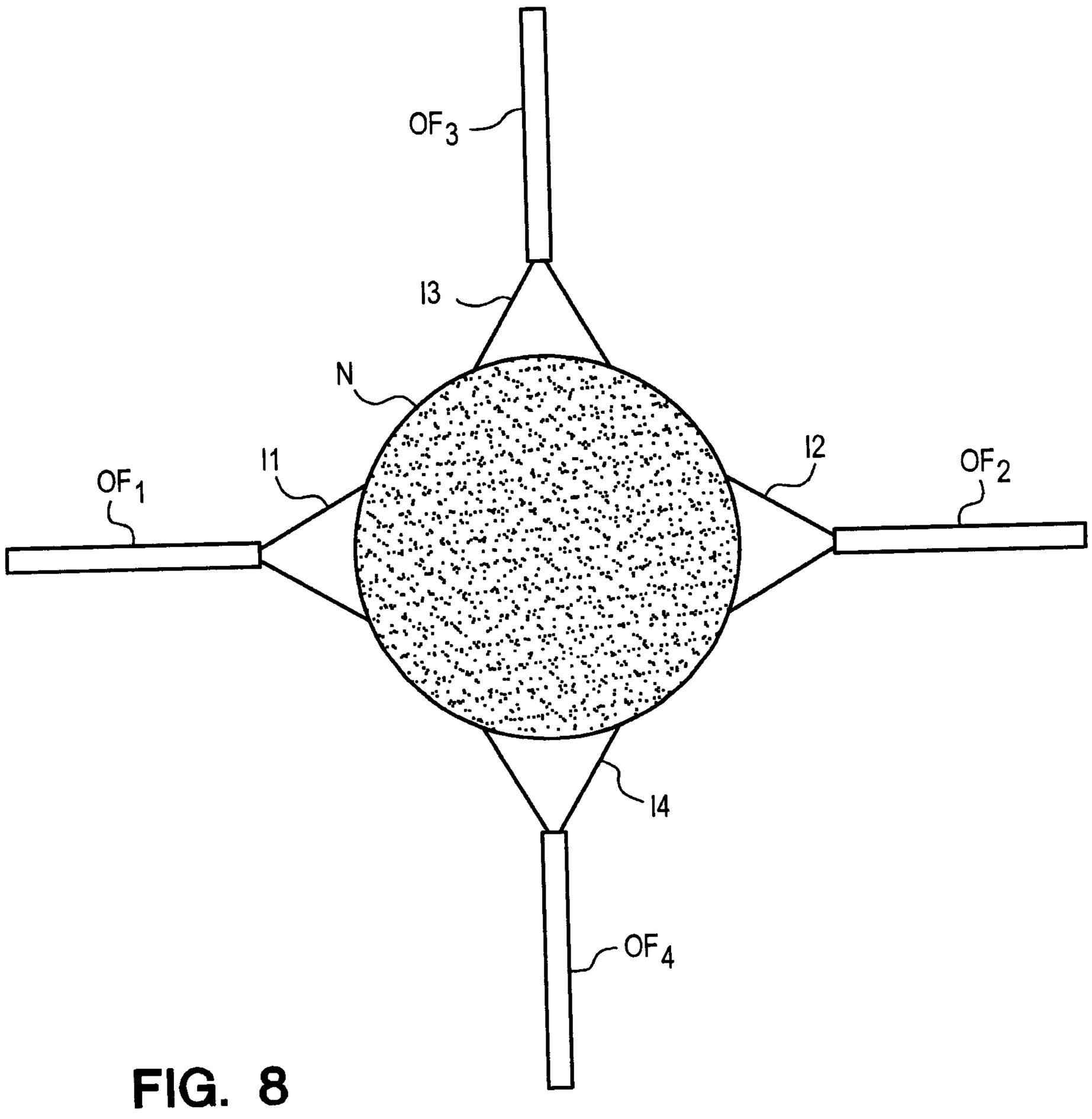

FIG. 8

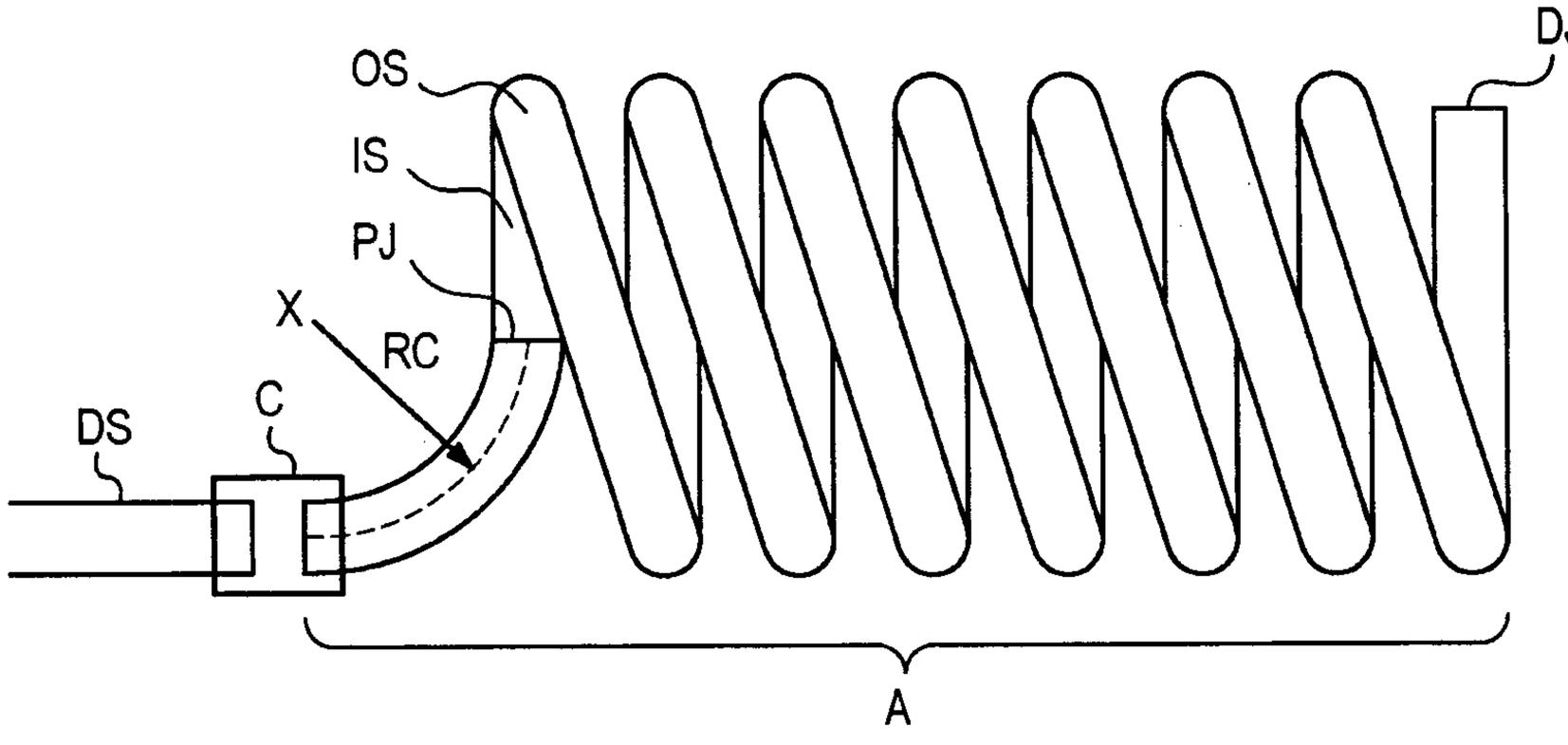

FIG. 9A

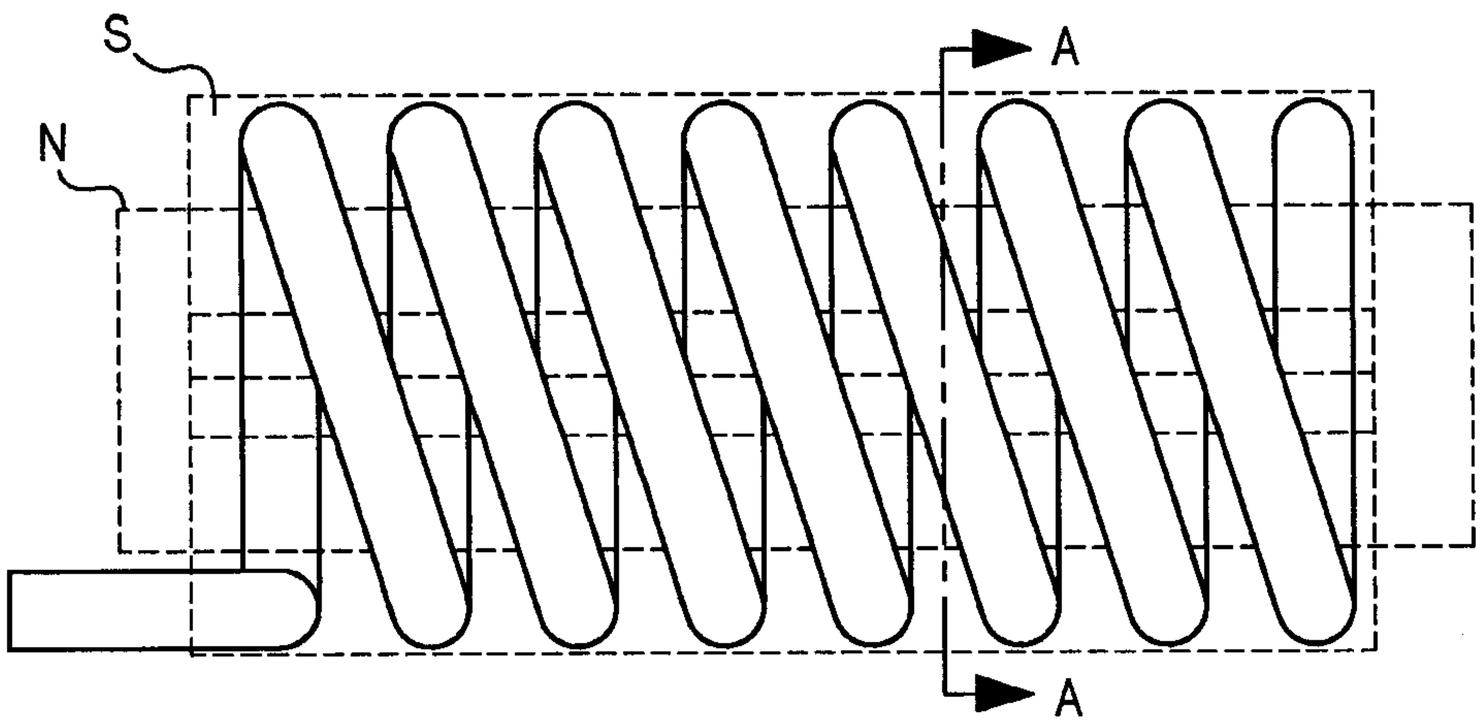

FIG. 9B

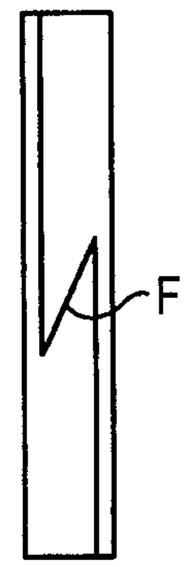

FIG. 9C

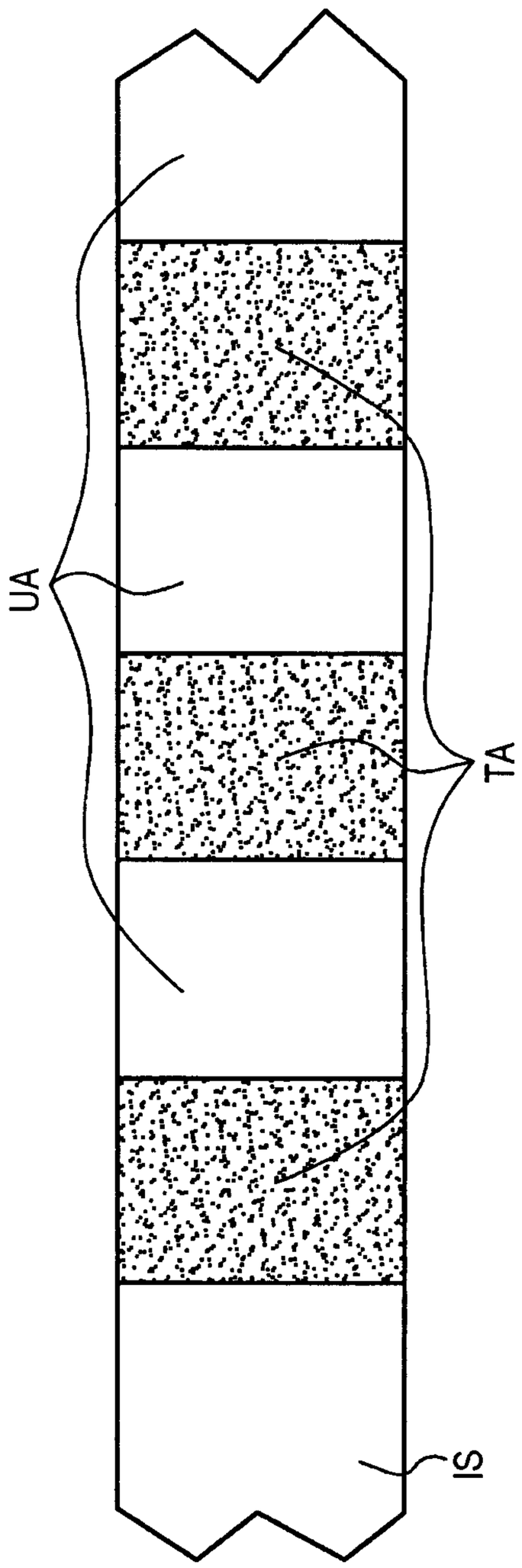

FIG. 10A

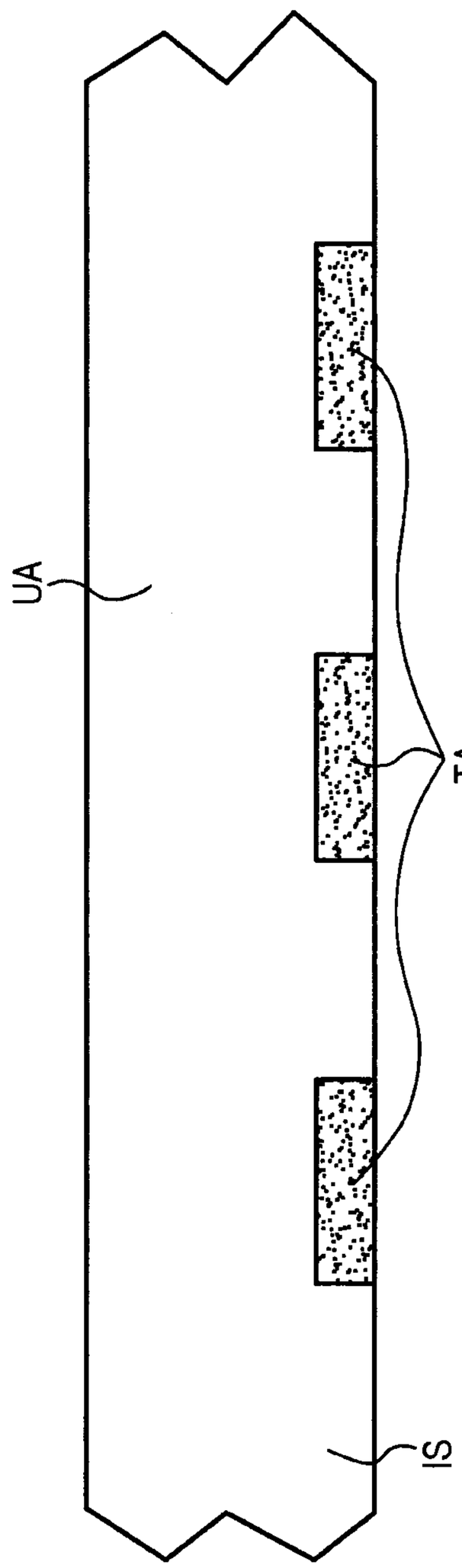

FIG. 10B

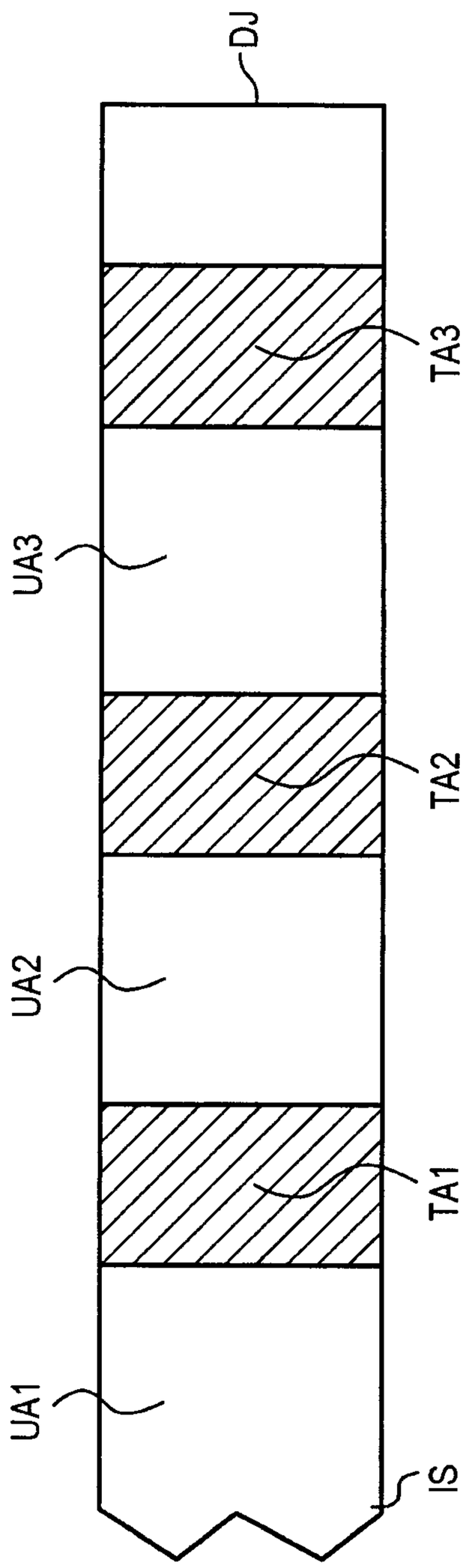

FIG. 10C

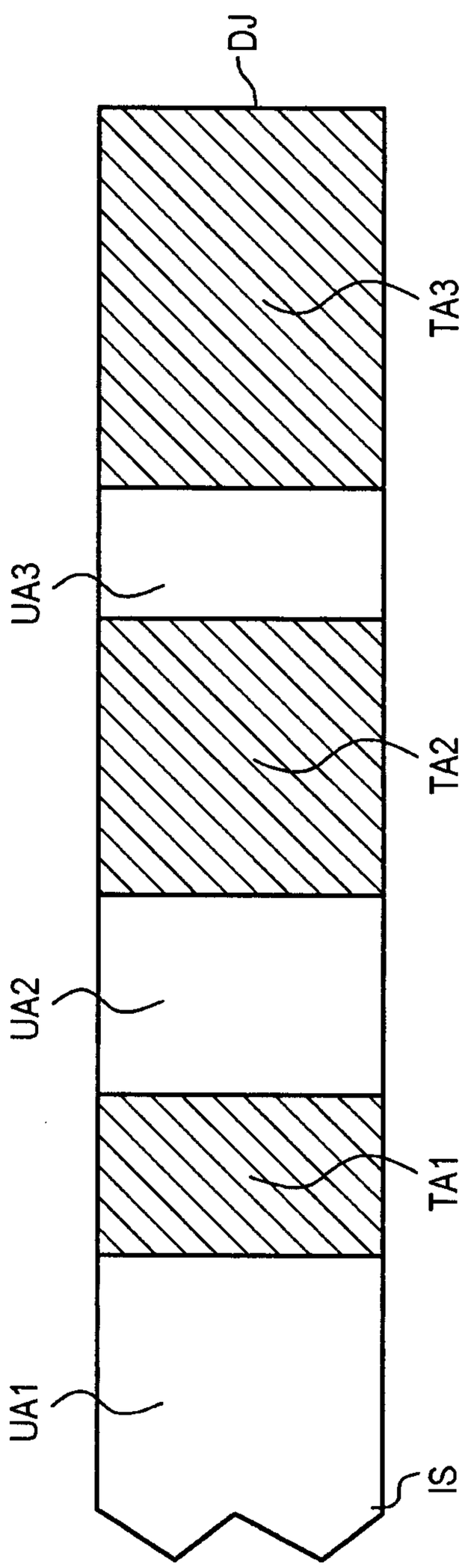

FIG. 10D

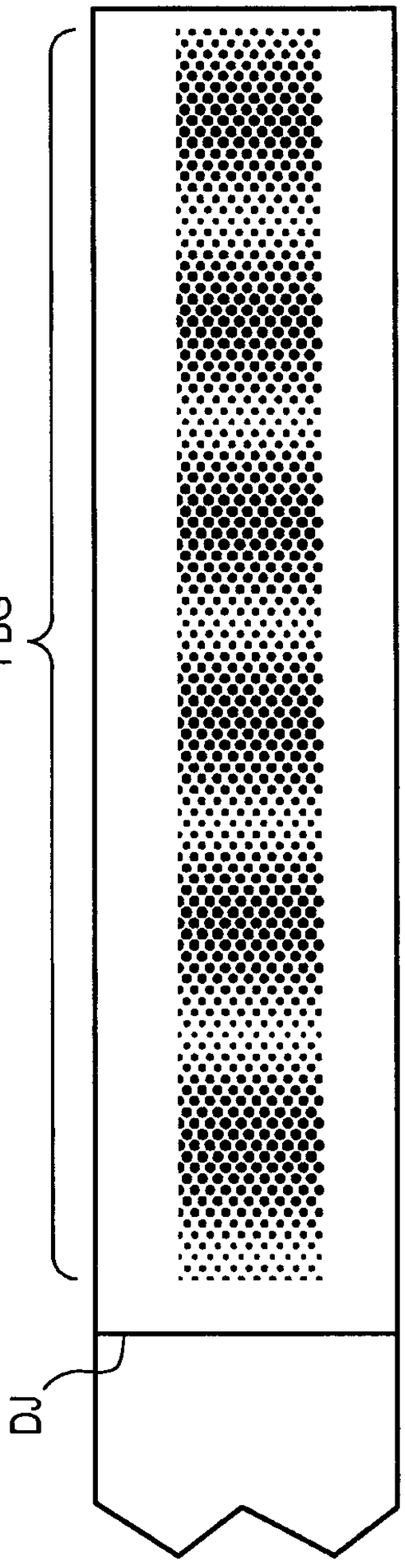

FIG. 11

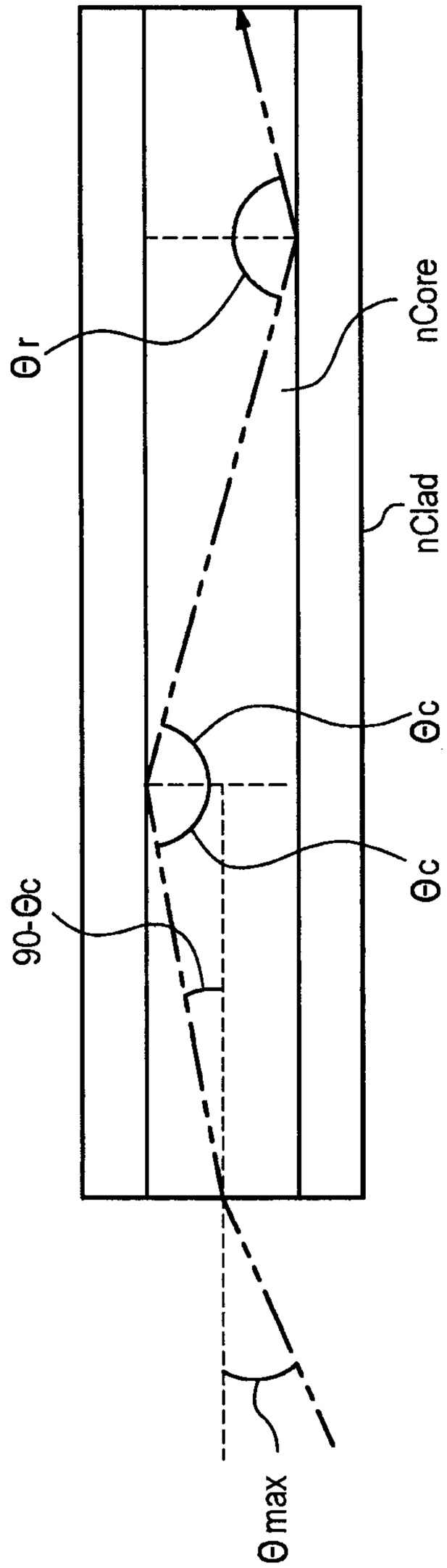

FIG. 12

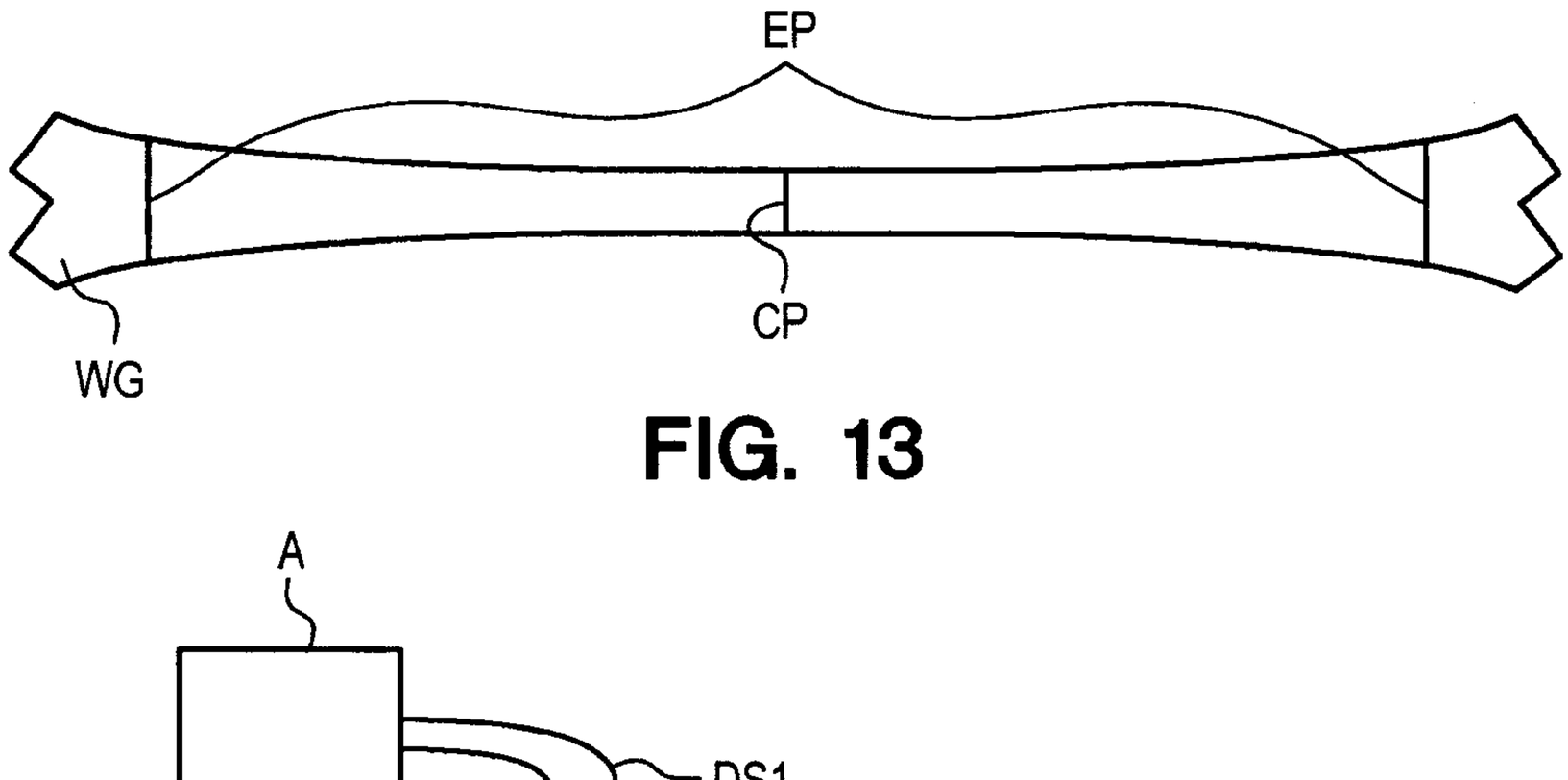

FIG. 14

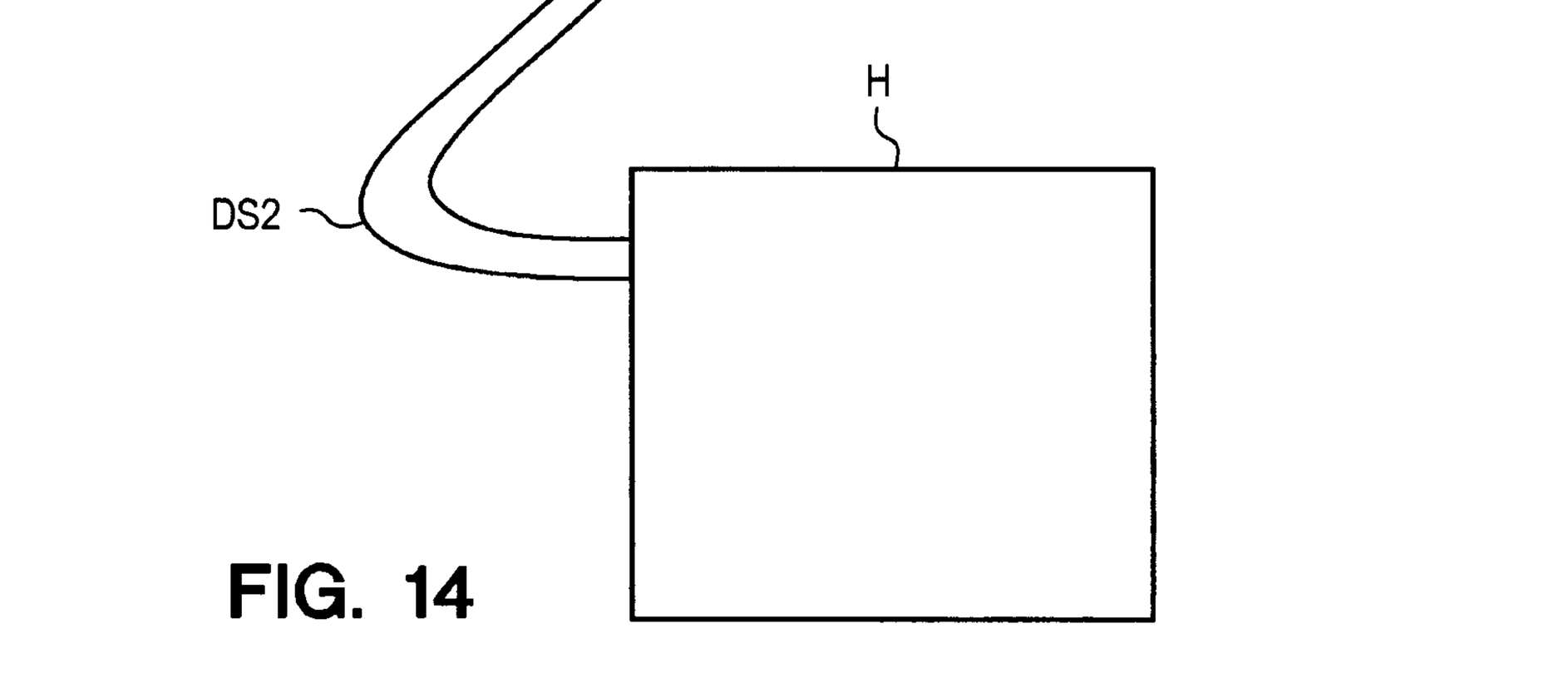

FIG. 15

FIG. 16A

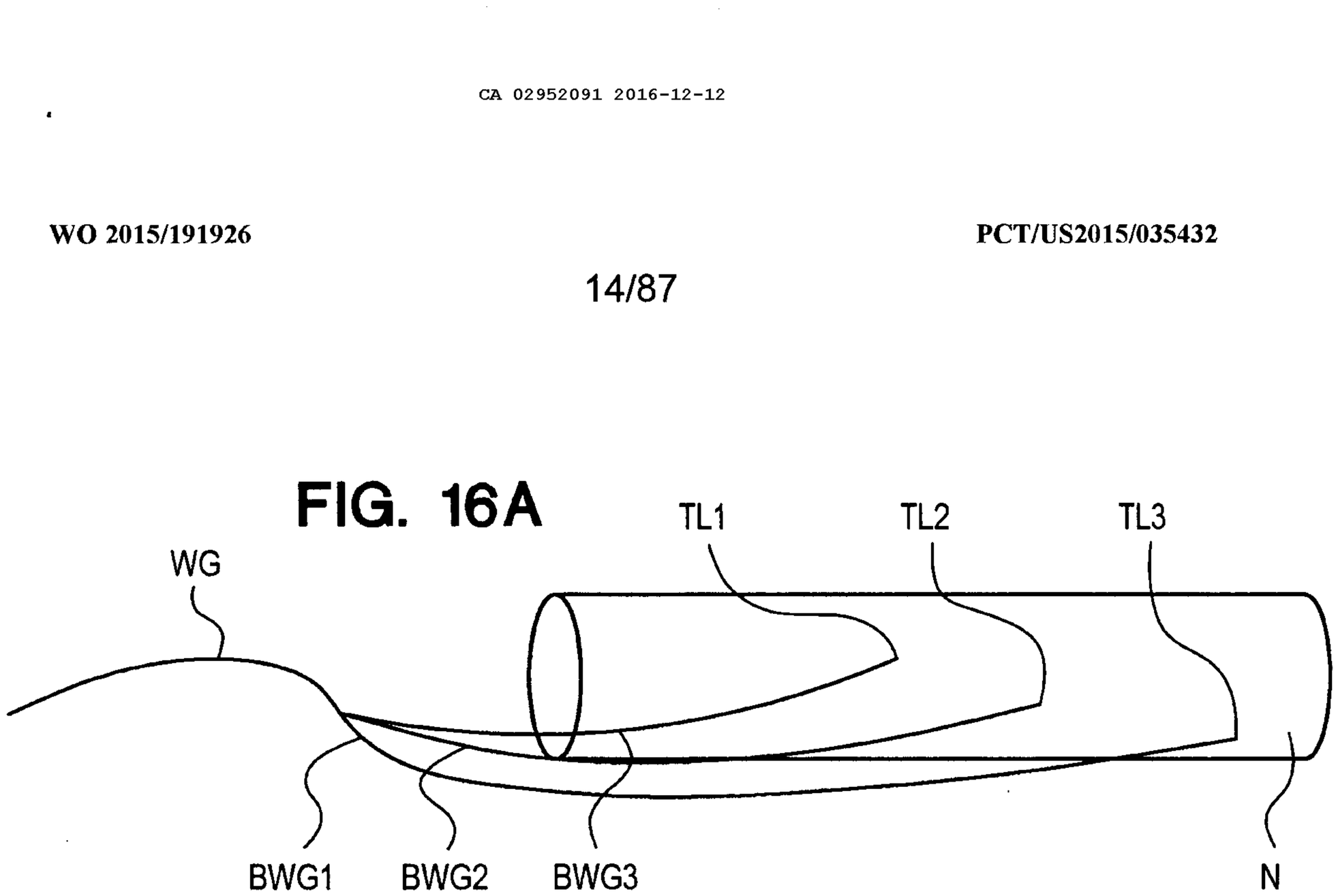

FIG. 16B

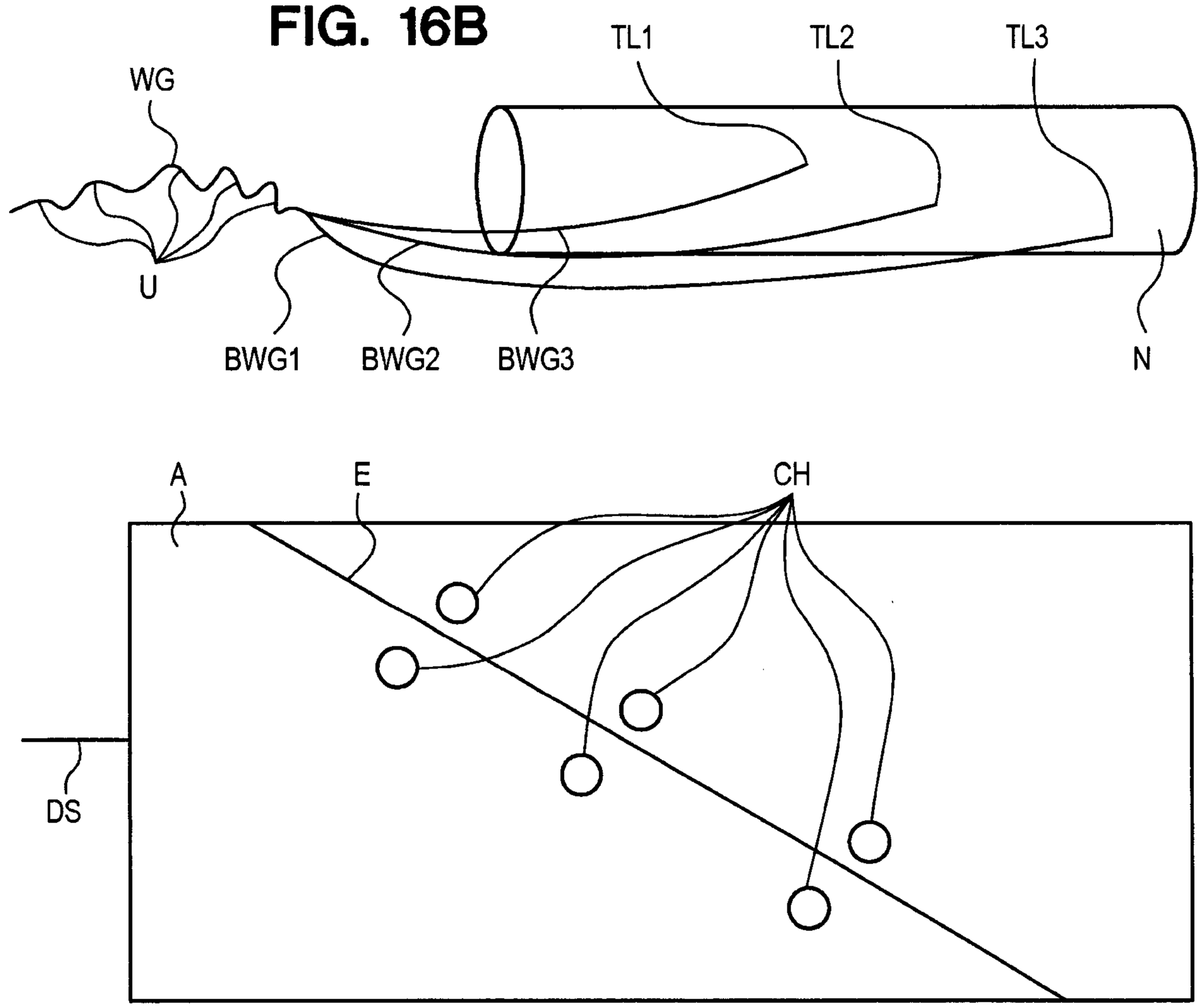

FIG. 17

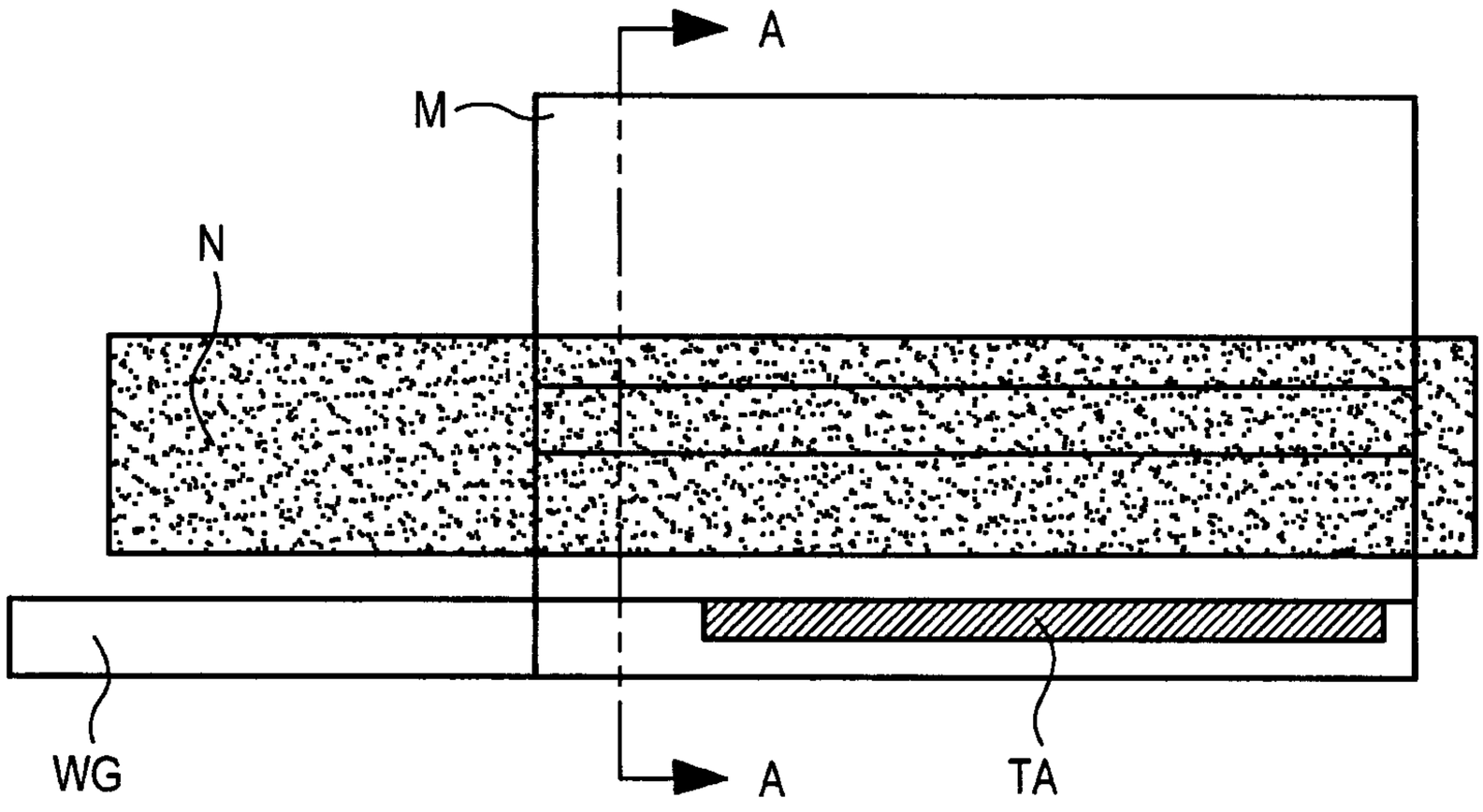

FIG. 18A

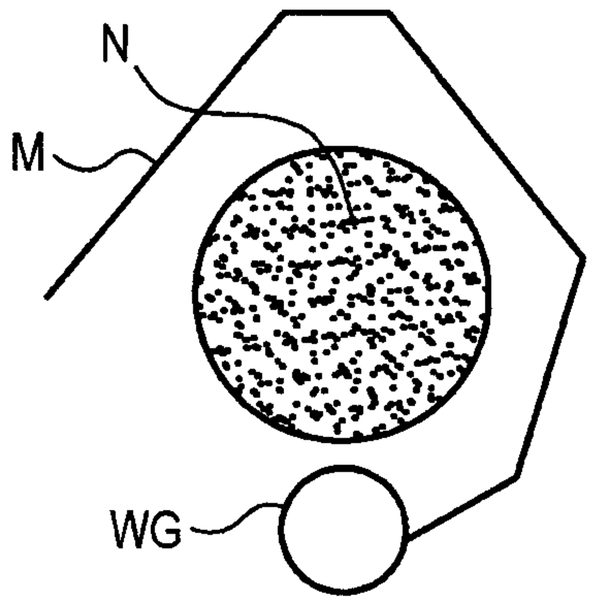

FIG. 18B

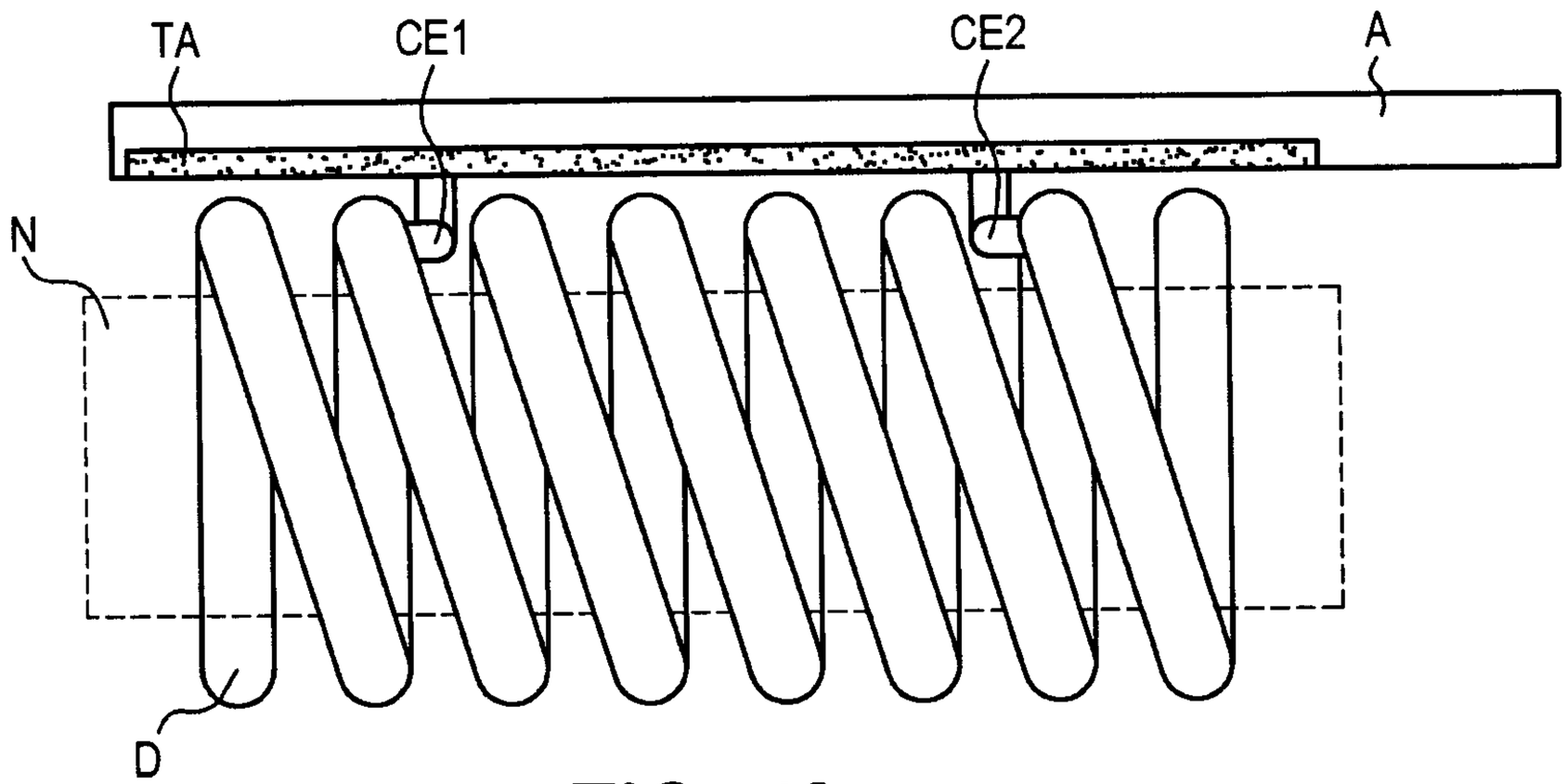

FIG. 19

FIG. 20A

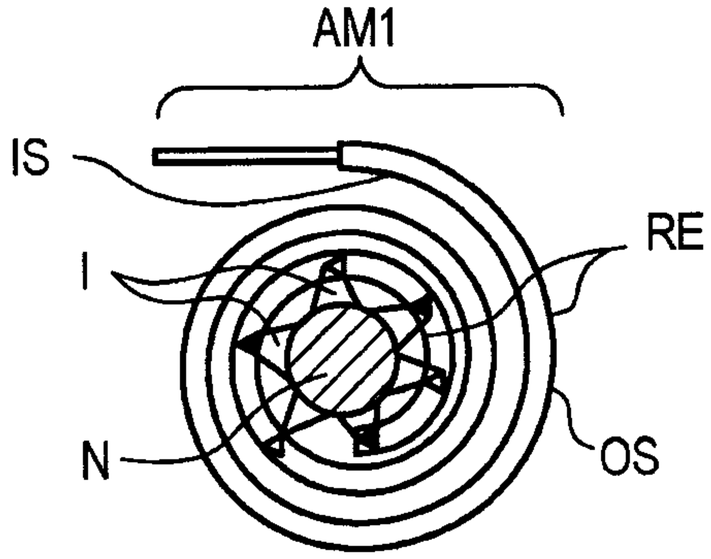

FIG. 20B

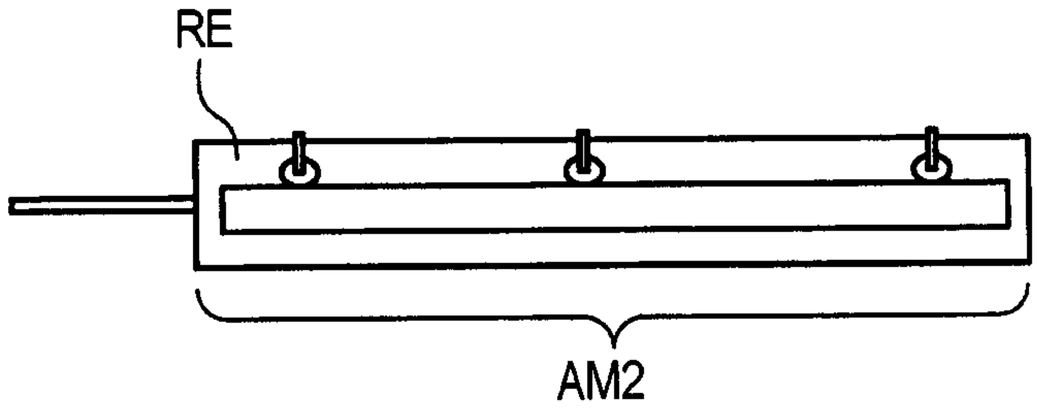

FIG. 20C

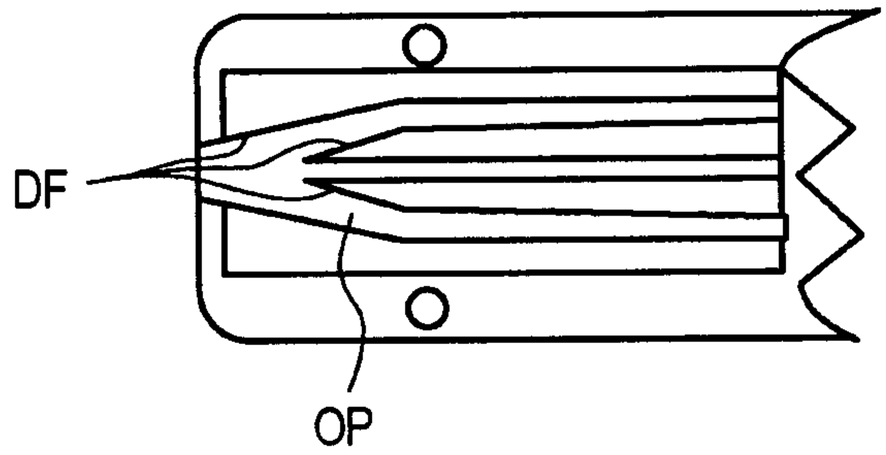

FIG. 21

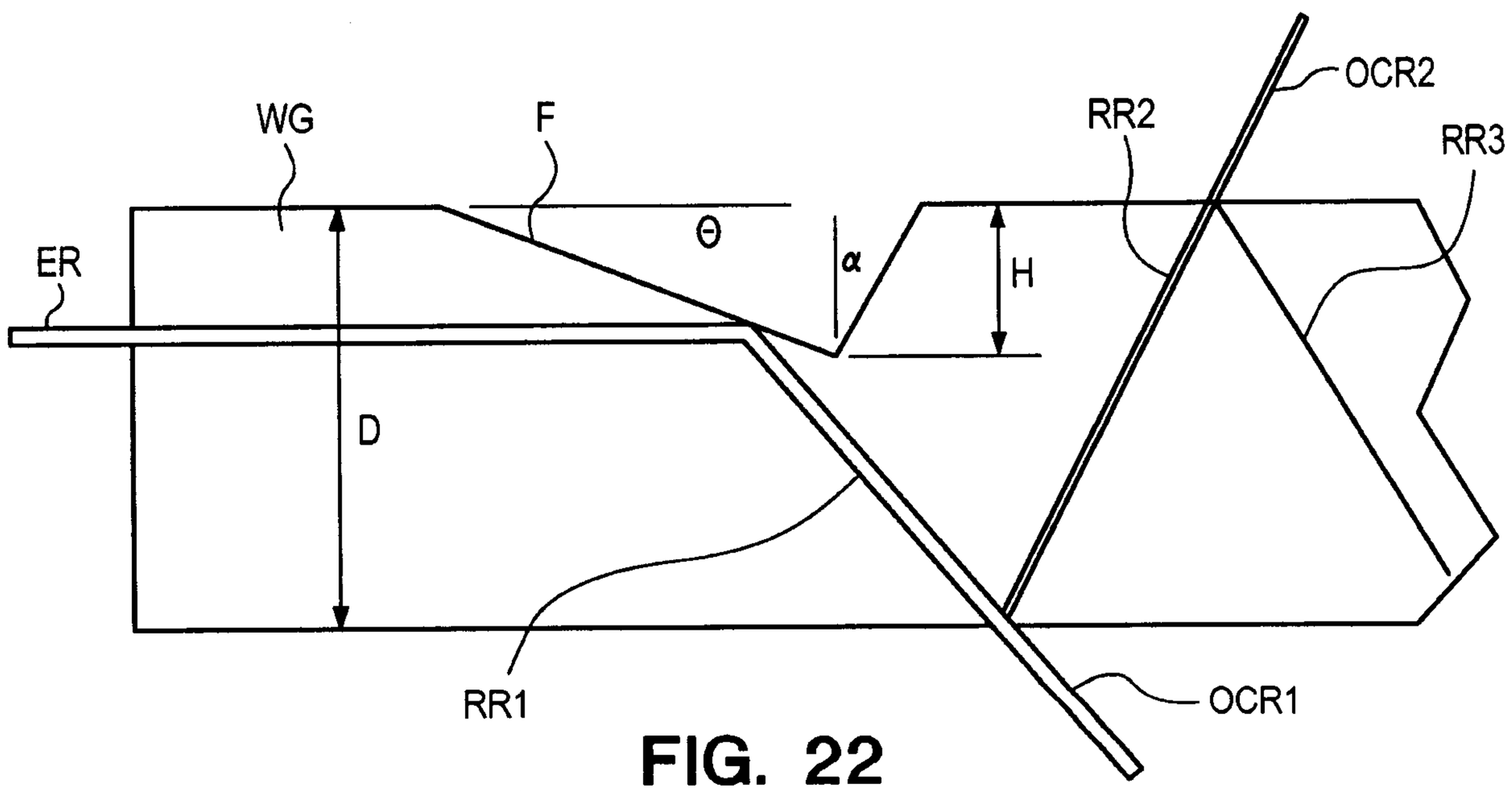

FIG. 22

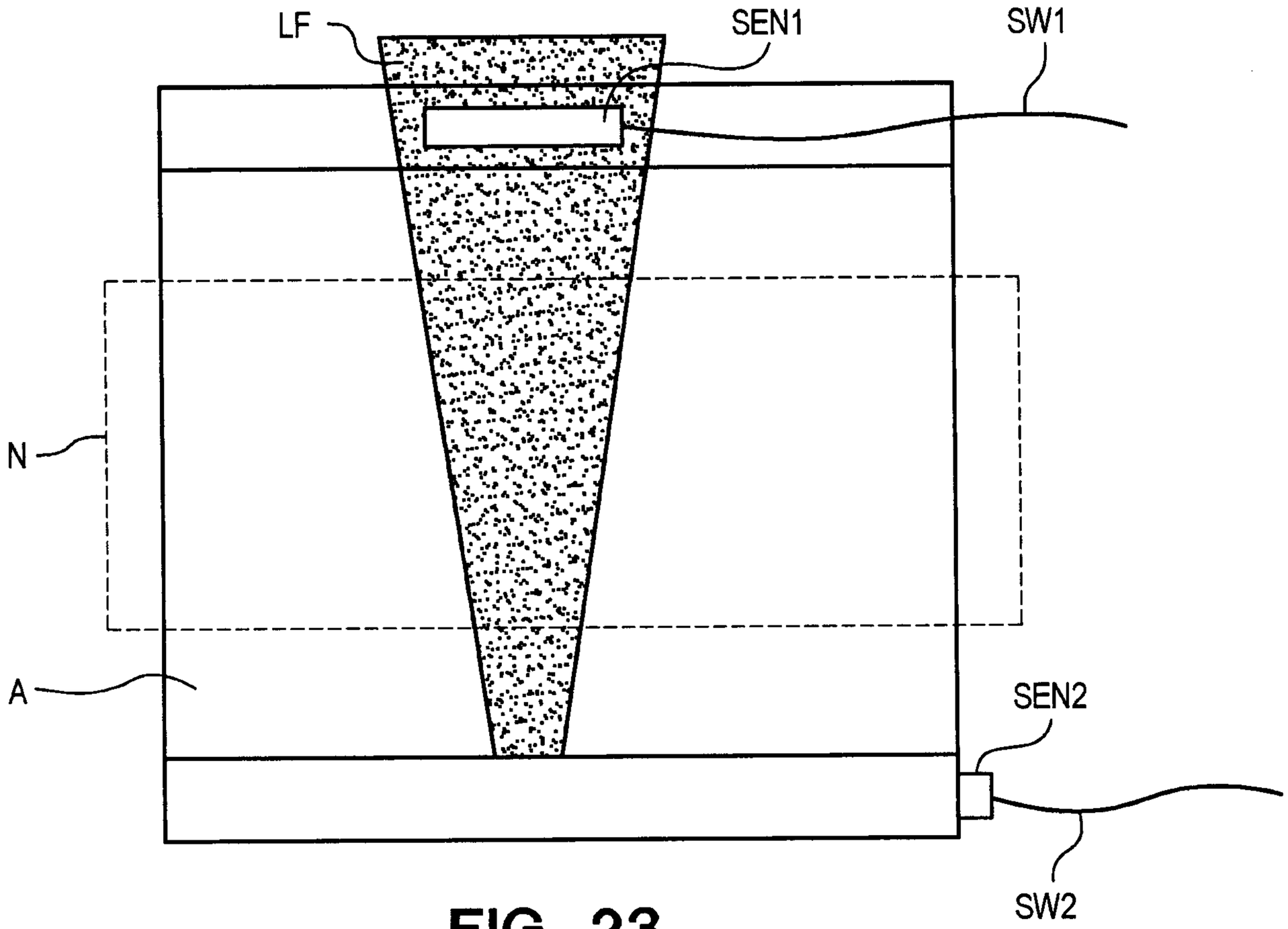

FIG. 23

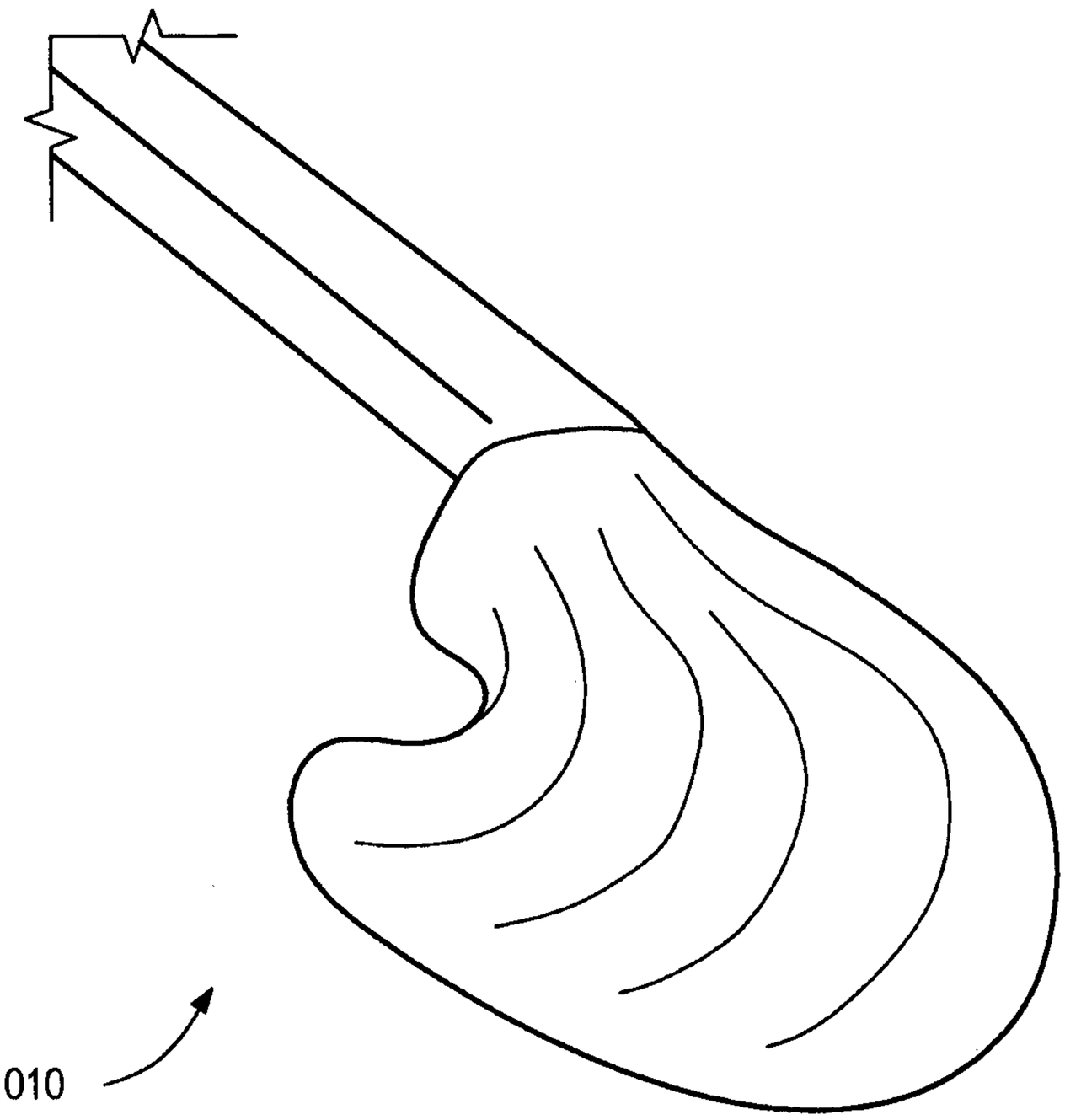

FIG. 24

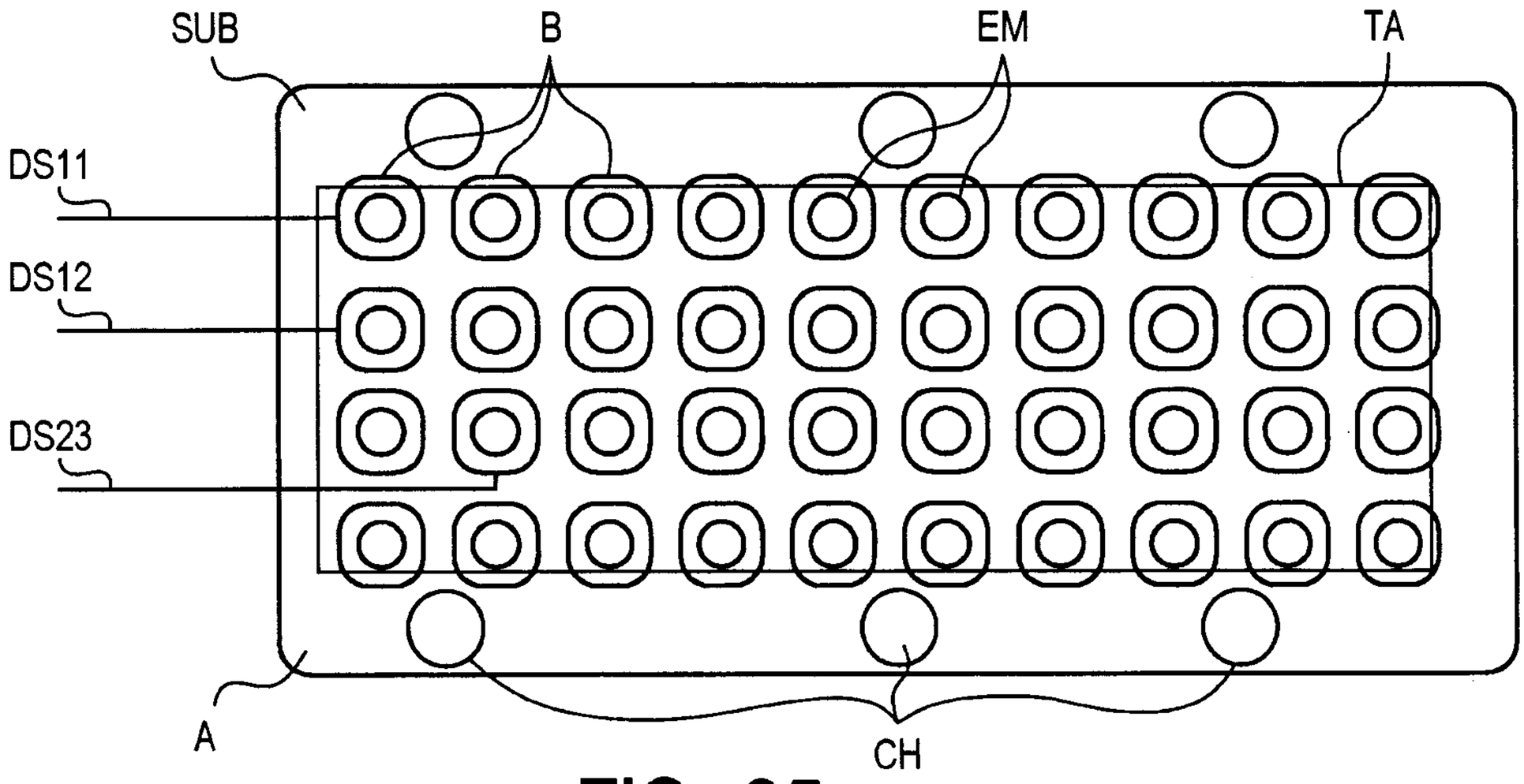

FIG. 25

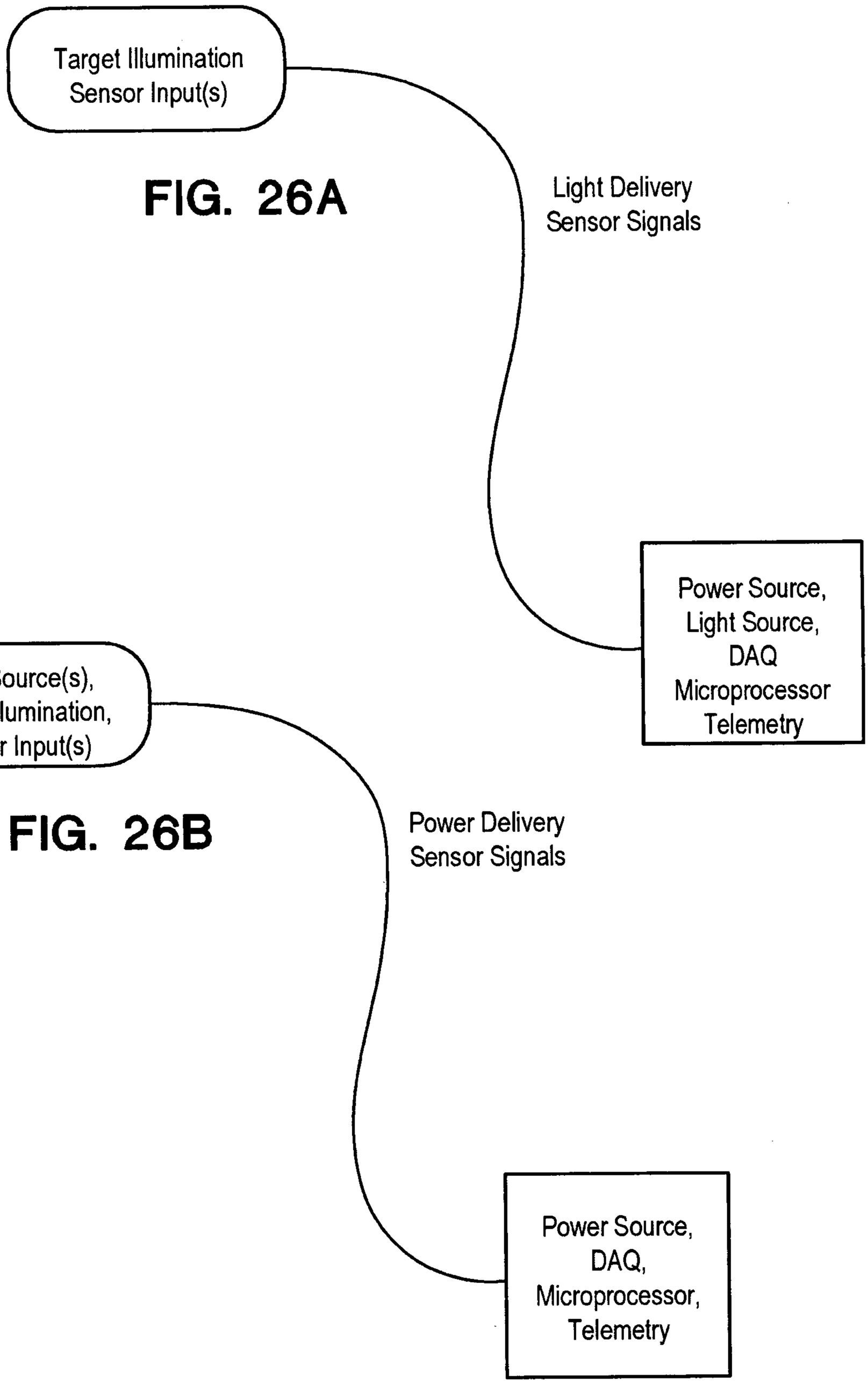

FIG. 26A

FIG. 26B

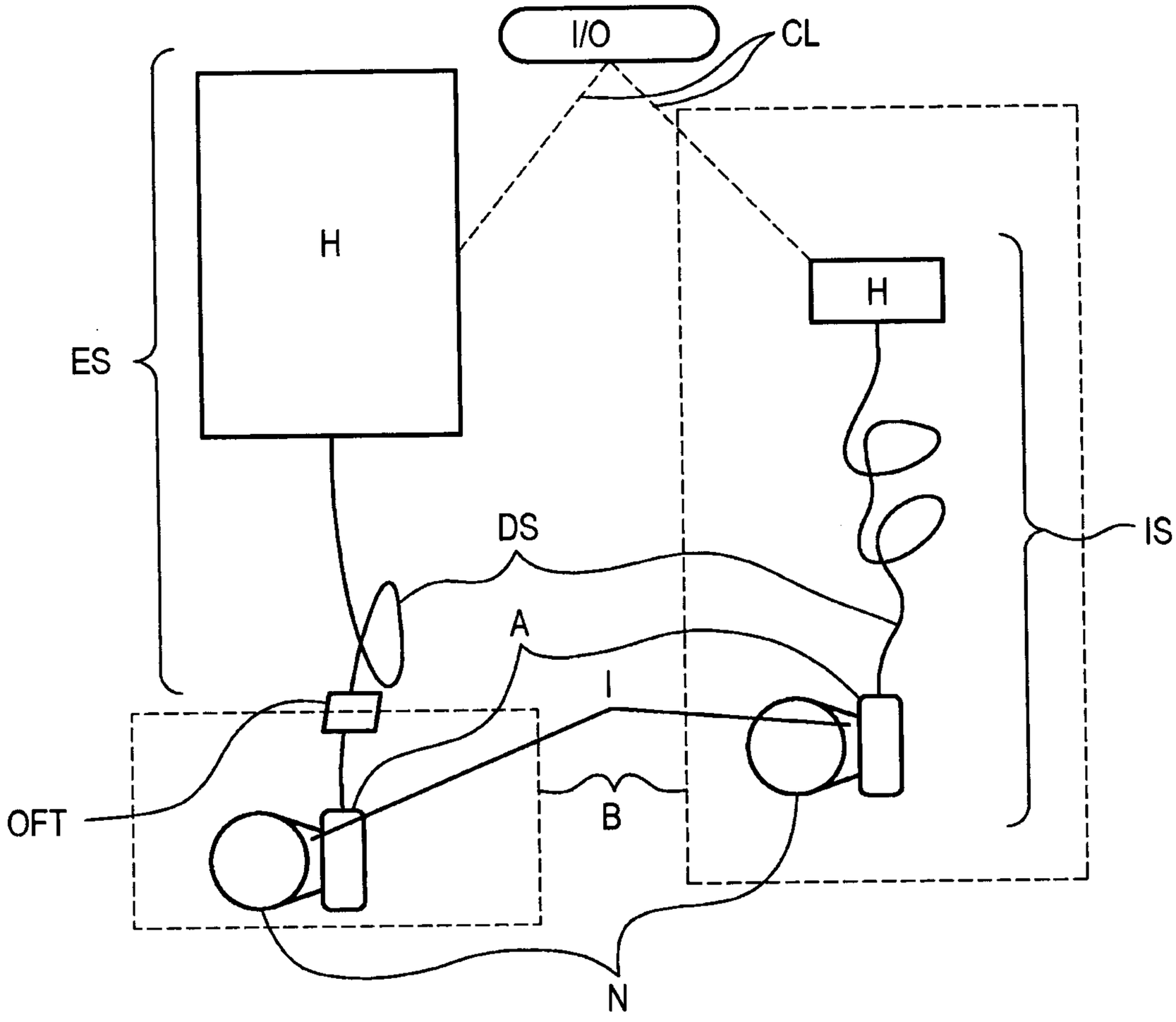

FIG. 27

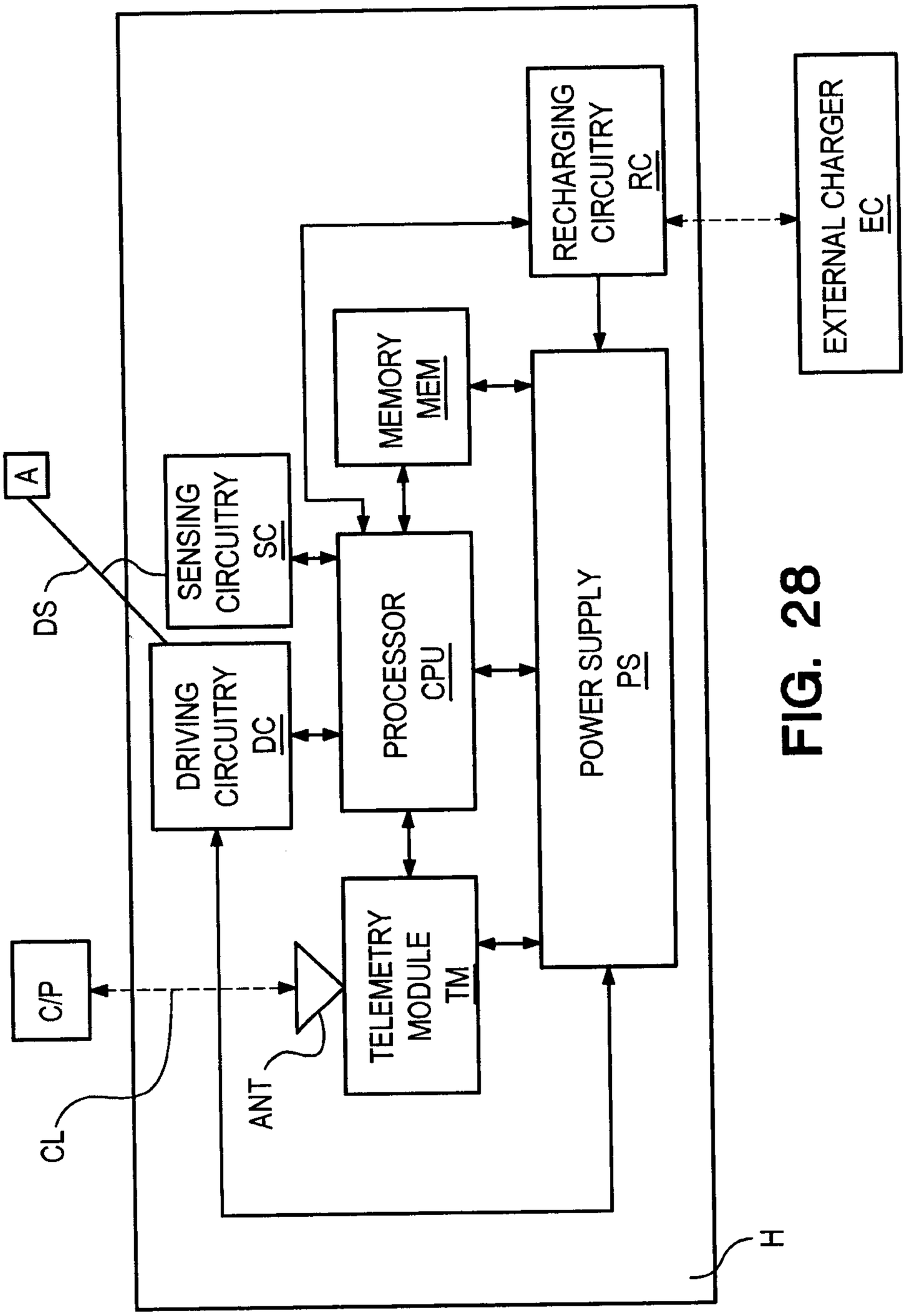
A
DS
SENSING CIRCUITRY SC
DRIVING CIRCUITRY DC
MEMORY MEM
PROCESSOR CPU
RECHARGING CIRCUITRY RC
POWER SUPPLY PS
EXTERNAL CHARGER EC
C/P
CL
ANT
TELEMETRY MODULE TM
I

FIG. 28

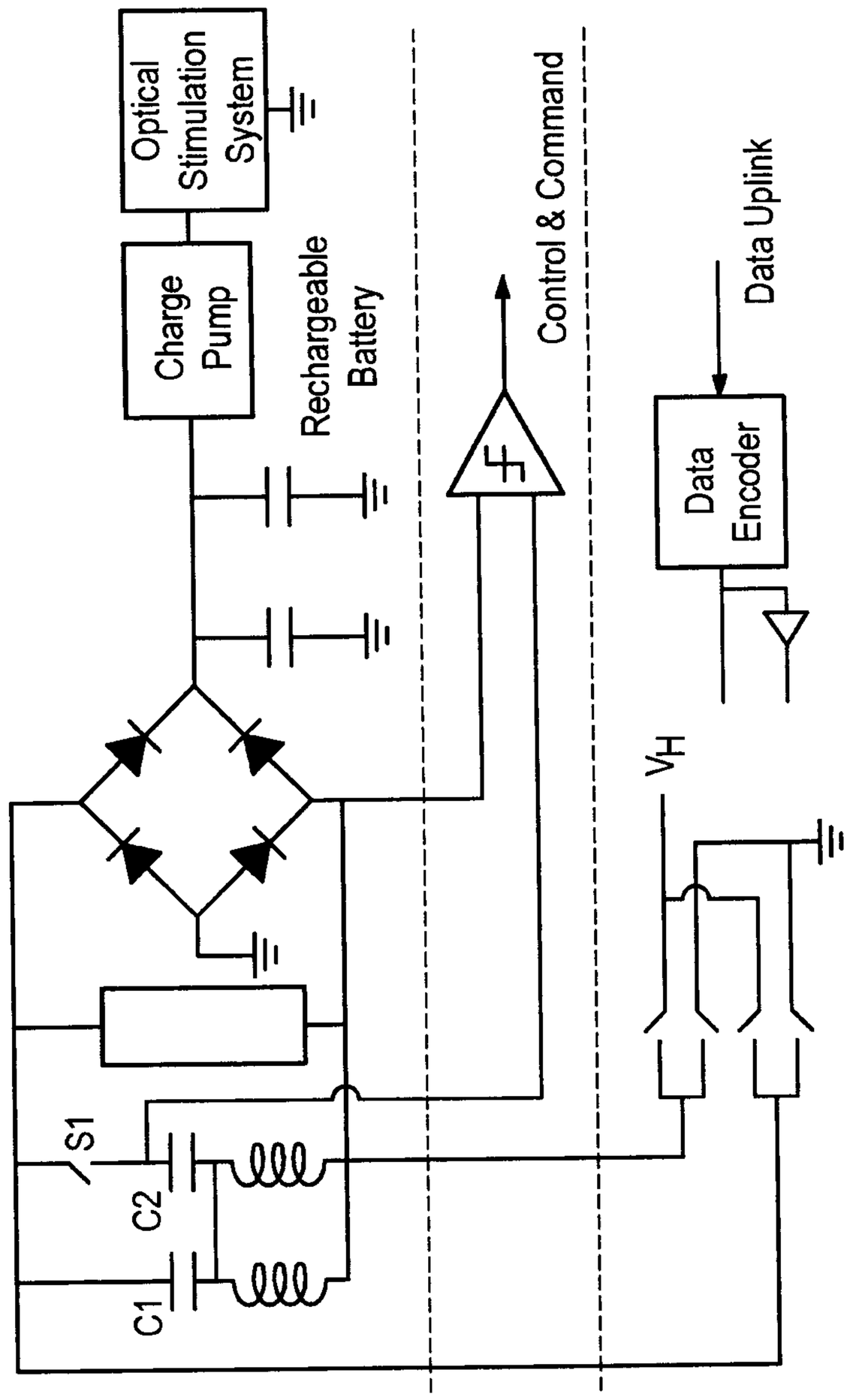
Optical Stimulation System
Charge Pump
Rechargeable Battery
Control & Command
Data Encoder
Data Uplink
V_H
S1
C2
C1

FIG. 29

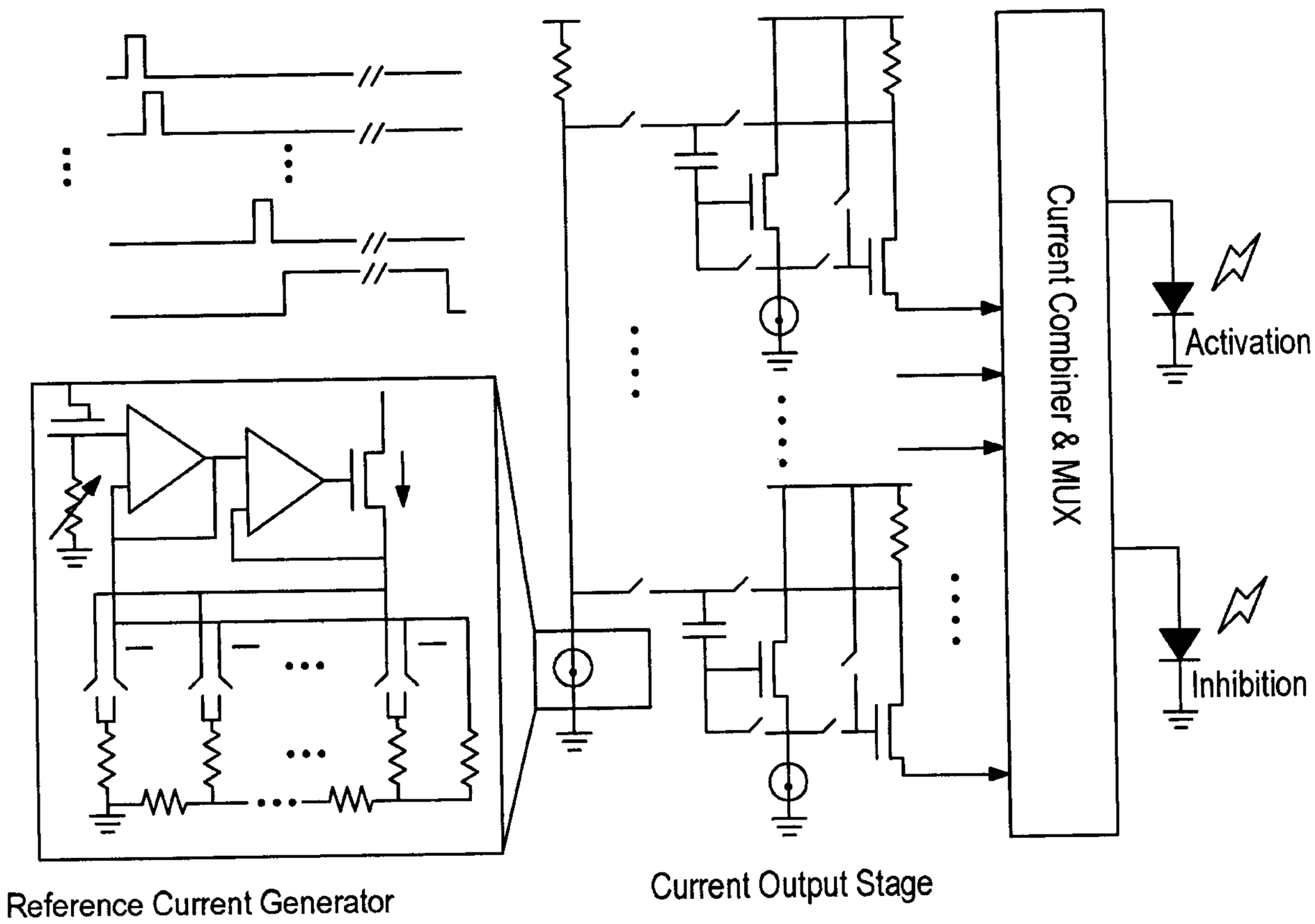
Current Combiner & MUX
Activation
Inhibition
Reference Current Generator
Current Output Stage

FIG. 30

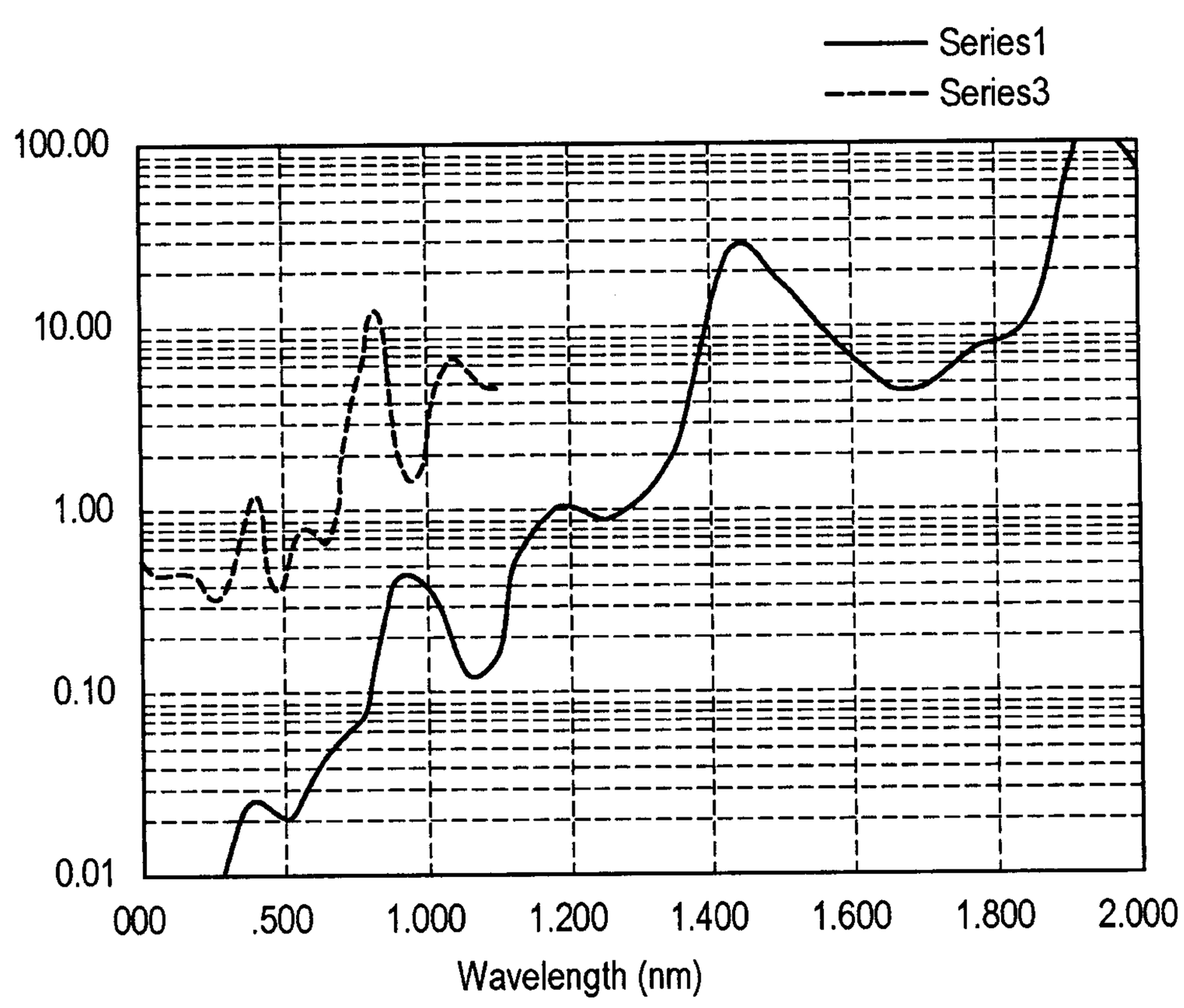
Series1
Series3
100.00
10.00
1.00
0.10
0.01
000
.500
1.000
1.200
1.400
1.600
1.800
2.000
Wavelength (nm)
1018

FIG. 31

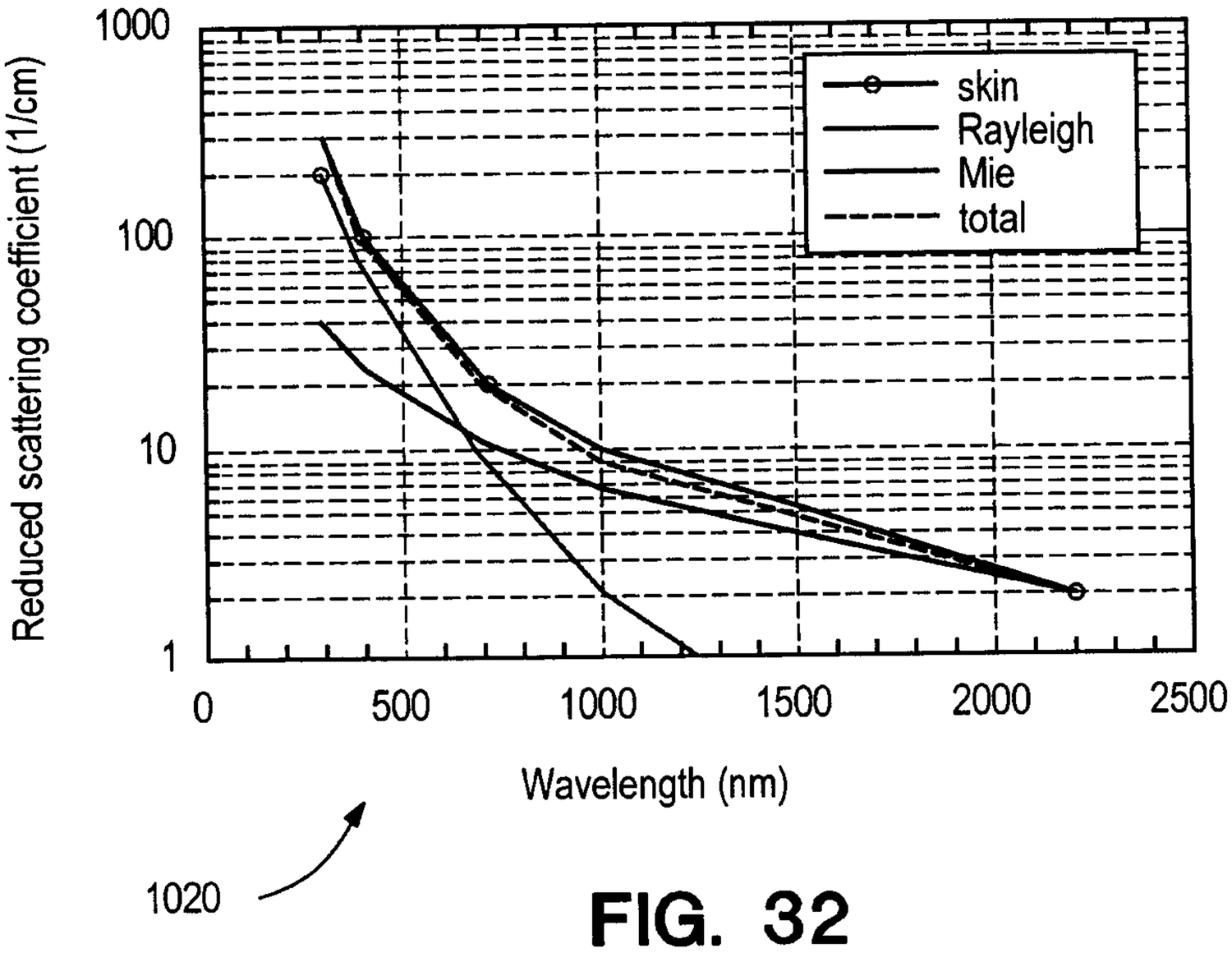
1000
100
10
1
Reduced scattering coefficient (1/cm)
0
500
1000
1500
2000
2500
Wavelength (nm)
skin
Rayleigh
Mie
total
1020

FIG. 32

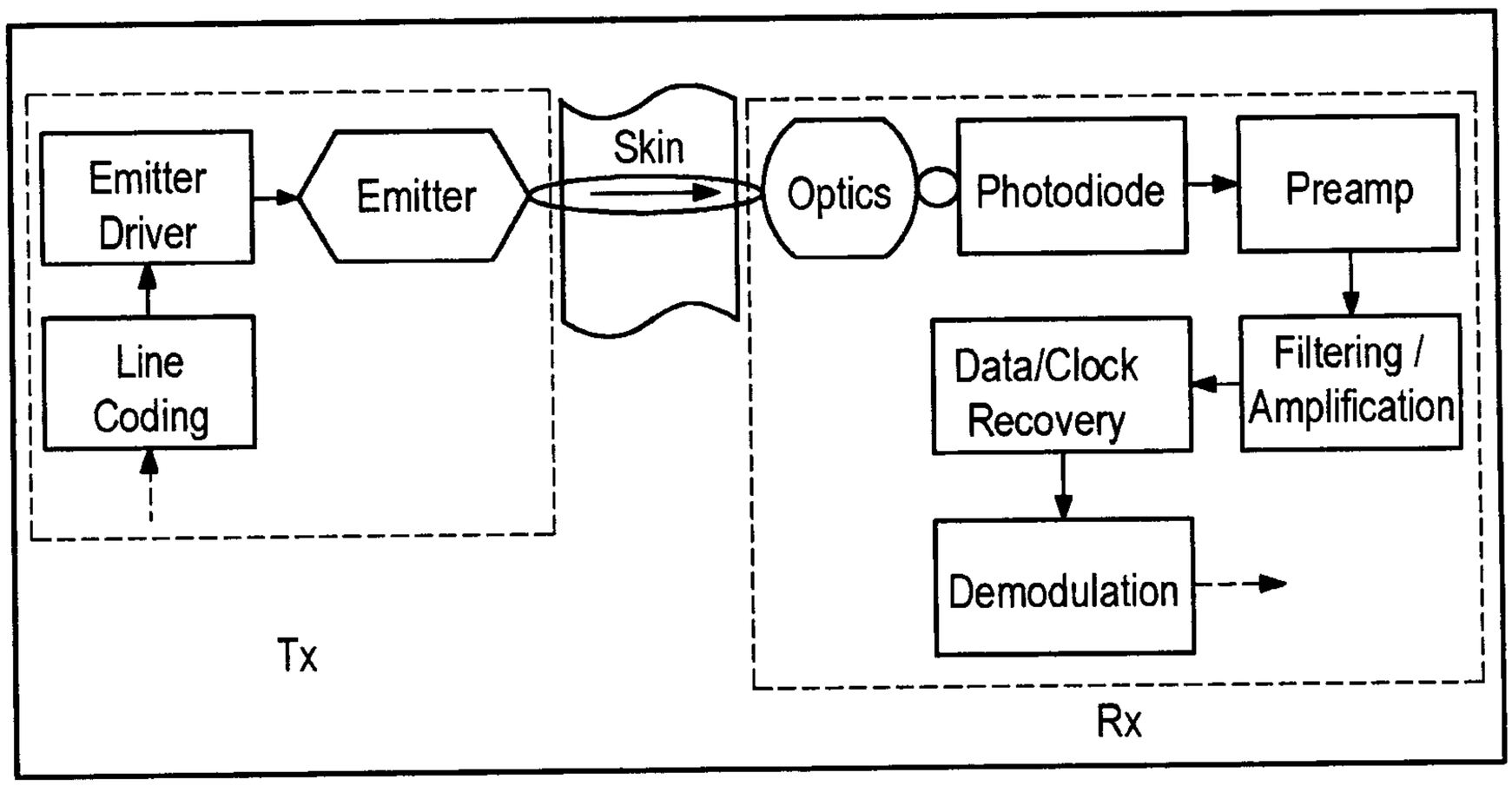
Emitter Driver
Line Coding
Emitter
Skin
Optics
Photodiode
Preamp
Filtering / Amplification
Data/Clock Recovery
Demodulation
Tx
Rx
1022

FIG. 33

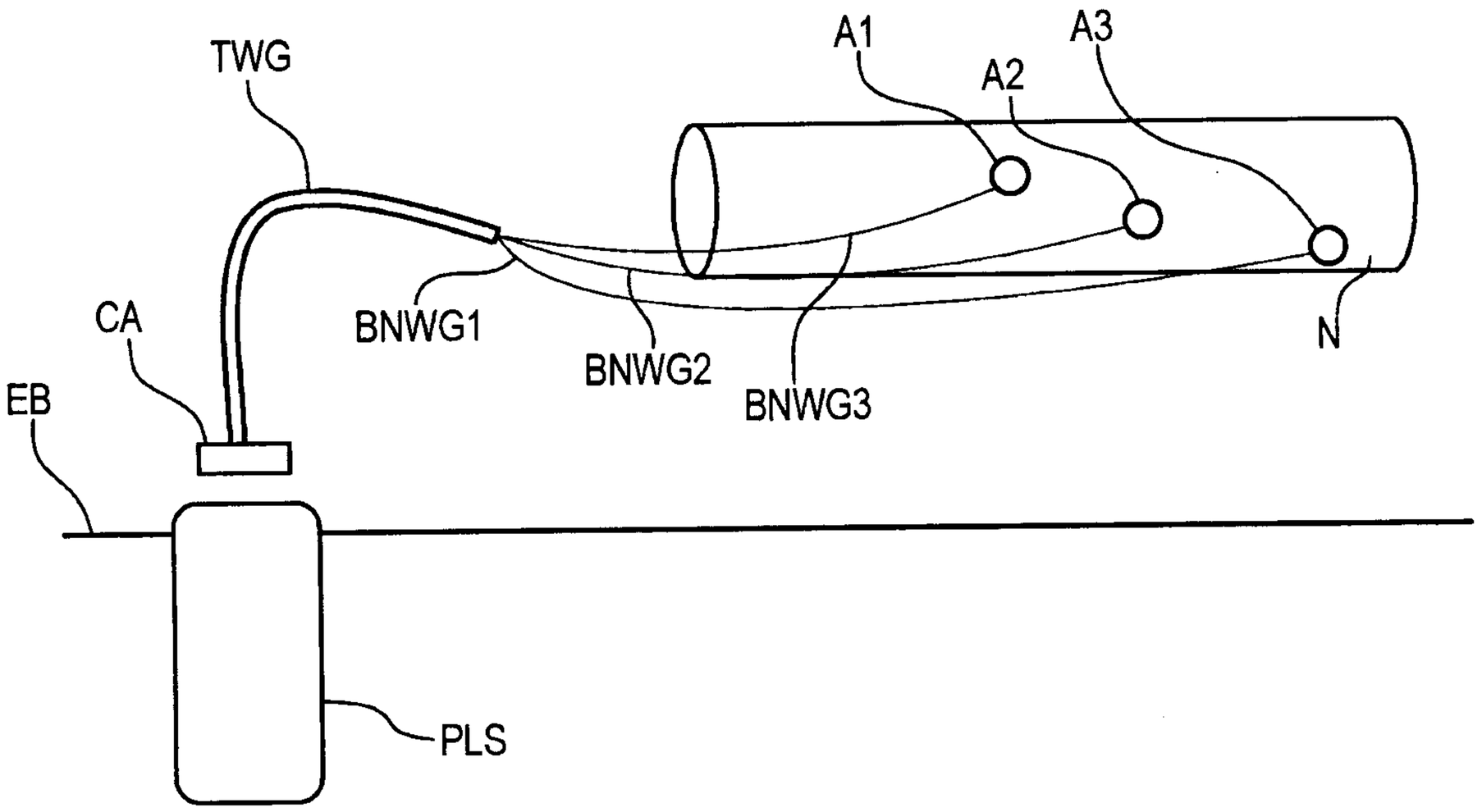
TWG
A1
A2
A3
CA
BNWG1
BNWG2
BNWG3
N
EB
PLS

FIG. 34

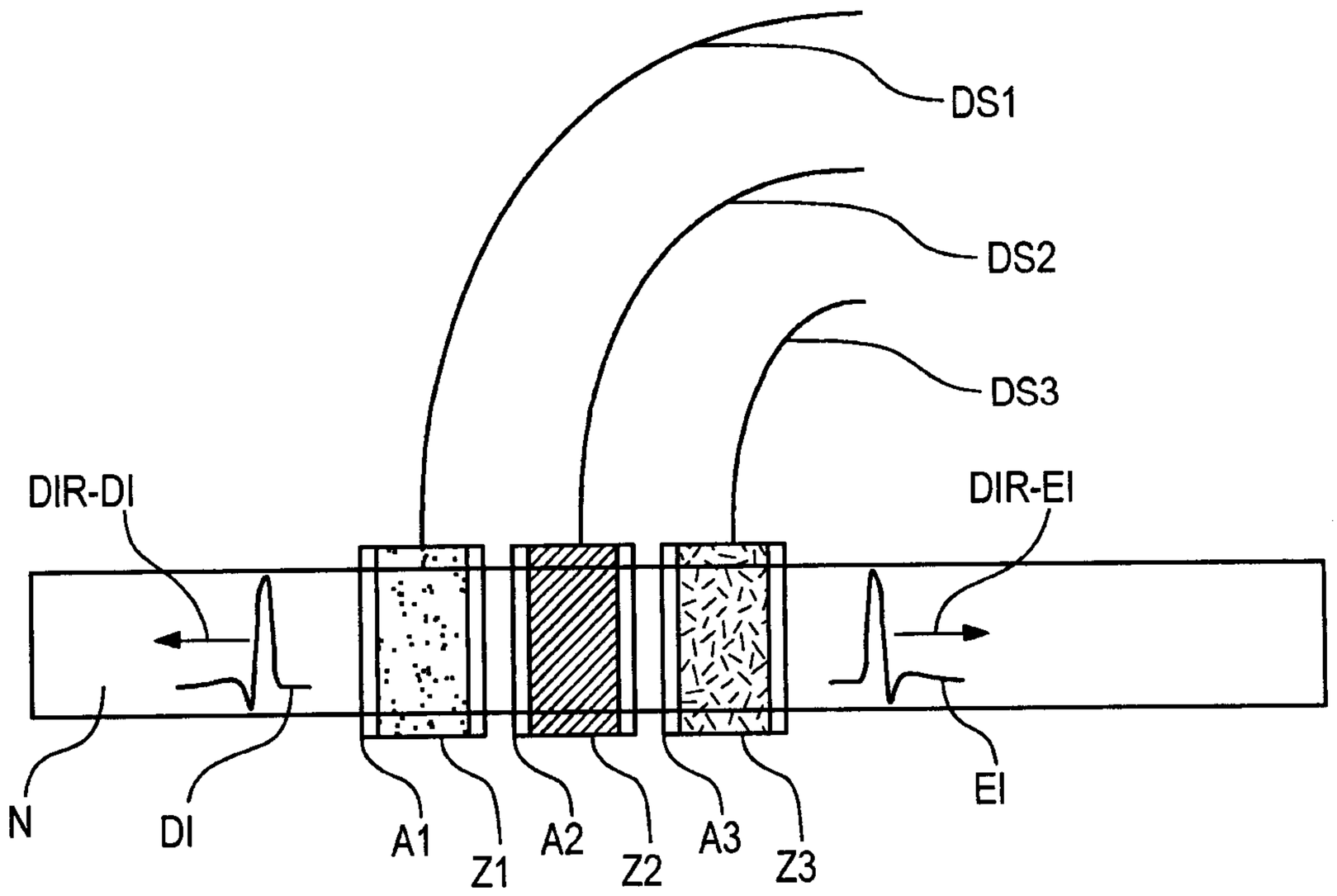
DS1
DS2
DS3
DIR-DI
DIR-EI
N
DI
A1
Z1
A2
Z2
A3
Z3
EI

FIG. 35

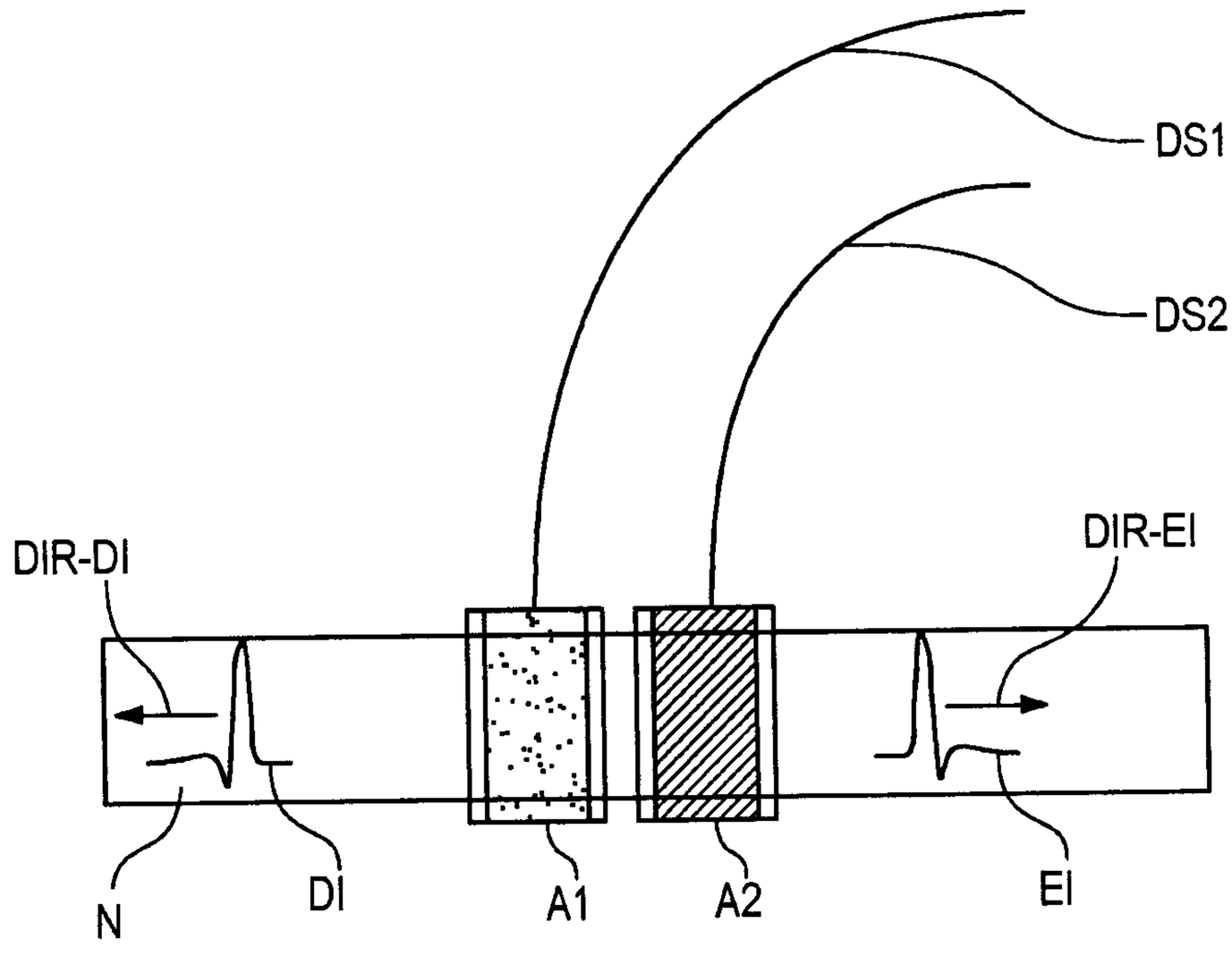

FIG. 36

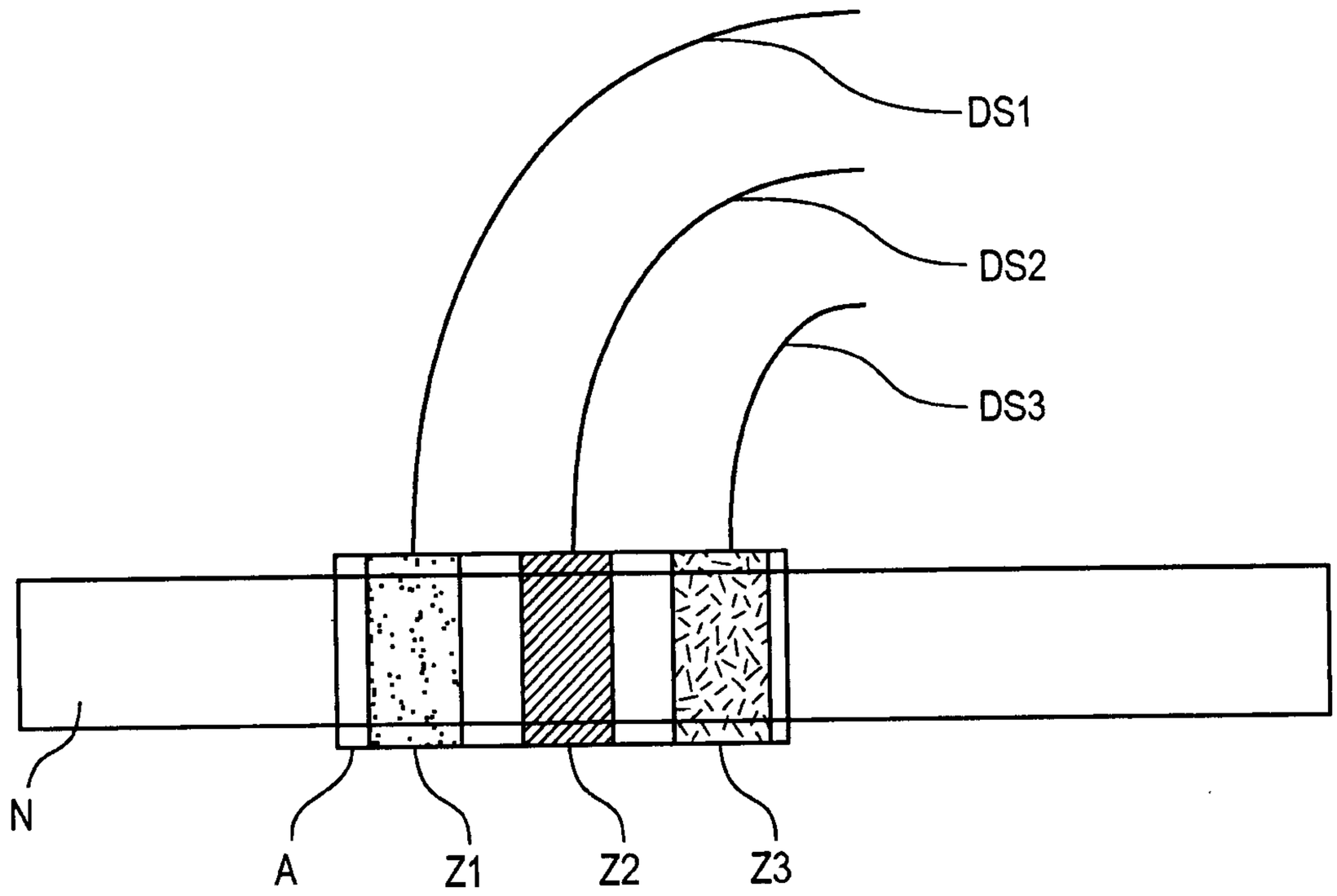

FIG. 37

ChR2 [gi|134153990|gb|AB064386.1] [SEQ ID NO: 1]
MDYGGALSAVGRELLFVTNPVVVNGSVLVPEDQCYCAGWIESRGTNGAQTASNVLQWLA
AGFSILLLMFY
AYQTWKSTCGWEEIYVCAIEMVKVILEFFFEFKNPSMLYLATGHRVQWLRYAEWLLTCP
VILIHLSNLTG
LSNDYSRRTMGLLVSDIGTIVWGATSAMATGYVKVIFFCLGLCYGANTFFHAAKAYIEG
YHTVPKGRCRQ
VVTGMAWLFFVSWGMFPILFILGPEGFGVLSVYGSTVGHTIIDLMSKNCWGLLGHYLRV
LIHEHILIHGD
IRKTTKLNIGGTEIEVETLVEDEAEAGAVP

FIG. 38A

ChR2 (C128A) [SFO] [SEQ ID NO: 2]
MDYGGALSAVGRELLFVTNPVVVNGSVLVPEDQCYCAGWIESRGTNGAQTASNVLQWLA
AGFSILLLMFY
AYQTWKSTCGWEEIYVCAIEMVKVILEFFFEFKNPSMLYLATGHRVQWLRYAEWLLTAP
VILIHLSNLTG
LSNDYSRRTMGLLVSDIGTIVWGATSAMATGYVKVIFFCLGLCYGANTFFHAAKAYIEG
YHTVPKGRCRQ
VVTGMAWLFFVSWGMFPILFILGPEGFGVLSVYGSTVGHTIIDLMSKNCWGLLGHYLRV
LIHEHILIHGD
IRKTTKLNIGGTEIEVETLVEDEAEAGAVP

FIG. 38B

ChR2 (C128S) [SFO] [SEQ ID NO: 3]
MDYGGALSAVGRELLFVTNPVVVNGSVLVPEDQCYCAGWIESRGTNGAQTASNVLQWLA
AGFSILLLMFY
AYQTWKSTCGWEEIYVCAIEMVKVILEFFFEFKNPSMLYLATGHRVQWLRYAEWLLTSP
VILIHLSNLTG
LSNDYSRRTMGLLVSDIGTIVWGATSAMATGYVKVIFFCLGLCYGANTFFHAAKAYIEG
YHTVPKGRCRQ
VVTGMAWLFFVSWGMFPILFILGPEGFGVLSVYGSTVGHTIIDLMSKNCWGLLGHYLRV
LIHEHILIHGD
IRKTTKLNIGGTEIEVETLVEDEAEAGAVP

FIG. 38C

ChR2 (C128T) [SFO] [SEQ ID NO: 4]
MDYGGALSAVGRELLFVTNPVVVNGSVLVPEDQCYCAGWIESRGTNGAQTASNVLQWLA
AGFSILLLMFY
AYQTWKSTCGWEEIYVCAIEMVKVILEFFFEFKNPSMLYLATGHRVQWLRYAEWLLTTP
VILIHLSNLTG
LSNDYSRRTMGLLVSDIGTIVWGATSAMATGYVKVIFFCLGLCYGANTFFHAAKAYIEG
YHTVPKGRCRQ
VVTGMAWLFFVSWGMFPILFILGPEGFGVLSVYGSTVGHTIIDLMSKNCWGLLGHYLRV
LIHEHILIHGD
IRKTTKLNIGGTEIEVETLVEDEAEAGAVP

FIG. 38D

ChR2 (D156A) [SFO] [SEQ ID NO: 5]
MDYGGALSAVGRELLFVTNPVVVNGSVLVPEDQCYCAGWIESRGTNGAQTASNVLQWLA
AGFSILLLMFY
AYQTWKSTCGWEEIYVCAIEMVKVILEFFFEFKNPSMLYLATGHRVQWLRYAEWLLTCP
VILIHLSNLTG
LSNDYSRRTMGLLVSAIGTIVWGATSAMATGYVKVIFFCLGLCYGANTFFHAAKAYIEG
YHTVPKGRCRQ
VVTGMAWLFFVSWGMFPILFILGPEGFGVLSVYGSTVGHTIIDLMSKNCWGLLGHYLRV
LIHEHILIHGD
IRKTTKLNIGGTEIEVETLVEDEAEAGAVP

FIG. 38E

ChR2 (D156A/C128S) (SSFO) [SEQ ID NO: 6]
MDYGGALSAVGRELLFVTNPVVVNGSVLVPEDQCYCAGWIESRGTNGAQTASNVLQWLA
AGFSILLLMFY
AYQTWKSTCGWEEIYVCAIEMVKVILEFFFEFKNPSMLYLATGHRVQWLRYAEWLLTSP
VILIHLSNLTG
LSNDYSRRTMGLLVSAIGTIVWGATSAMATGYVKVIFFCLGLCYGANTFFHAAKAYIEG
YHTVPKGRCRQ
VVTGMAWLFFVSWGMFPILFILGPEGFGVLSVYGSTVGHTIIDLMSKNCWGLLGHYLRV
LIHEHILIHGD
IRKTTKLNIGGTEIEVETLVEDEAEAGAVP

FIG. 38F

ChR2 (T159C) [SEQ ID NO: 7]
MDYGGALSAVGRELLFVTNPVVVNGSVLVPEDQCYCAGWIESRGTNGAQTASNVLQWLA
AGFSILLLMFY
AYQTWKSTCGWEEIYVCAIEMVKVILEFFFEFKNPSMLYLATGHRVQWLRYAEWLLTCP
VILIHLSNLTG
LSNDYSRRTMGLLVSDIGCIVWGATSAMATGYVKVIFFCLGLCYGANTFFHAAKAYIEG
YHTVPKGRCRQ
VVTGMAWLFFVSWGMFPILFILGPEGFGVLSVYGSTVGHTIIDLMSKNCWGLLGHYLRV
LIHEHILIHGD
IRKTTKLNIGGTEIEVETLVEDEAEAGAVP

FIG. 38G

ChR2(L132C) (CatCH) [SEQ ID NO: 8]
MDYGGALSAVGRELLFVTNPVVVNGSVLVPEDQCYCAGWIESRGTNGAQTASNVLQWLA
AGFSILLLMFY
AYQTWKSTCGWEEIYVCAIEMVKVILEFFFEFKNPSMLYLATGHRVQWLRYAEWLLTCP
VICIHLSNLTG
LSNDYSRRTMGLLVSDIGTIVWGATSAMATGYVKVIFFCLGLCYGANTFFHAAKAYIEG
YHTVPKGRCRQ
VVTGMAWLFFVSWGMFPILFILGPEGFGVLSVYGSTVGHTIIDLMSKNCWGLLGHYLRV
LIHEHILIHGD
IRKTTKLNIGGTEIEVETLVEDEAEAGAVP

FIG. 38H

ChR2 (E123T/T159C) [SEQ ID NO: 9]
MDYGGALSAVGRELLFVTNPVVVNGSVLVPEDQCYCAGWIESRGTNGAQTASNVLQWLA
AGFSILLLMFY
AYQTWKSTCGWEEIYVCAIEMVKVILEFFFEFKNPSMLYLATGHRVQWLRYATWLLTCP
VILIHLSNLTG
LSNDYSRRTMGLLVSDIGCIVWGATSAMATGYVKVIFFCLGLCYGANTFFHAAKAYIEG
YHTVPKGRCRQ
VVTGMAWLFFVSWGMFPILFILGPEGFGVLSVYGSTVGHTIIDLMSKNCWGLLGHYLRV
LIHEHILIHGD
IRKTTKLNIGGTEIEVETLVEDEAEAGAVP

FIG. 38I

ChR2 (H134R) [SEQ ID NO: 10]
MDYGGALSAVGRELLFVTNPVVVNGSVLVPEDQCYCAGWIESRGTNGAQTASNVLQWLA
AGFSILLLMFY
AYQTWKSTCGWEEIYVCAIEMVKVILEFFFEFKNPSMLYLATGHRVQWLRYAEWLLTCP
VILIRLSNLTG
LSNDYSRRTMGLLVSDIGTIVWGATSAMATGYVKVIFFCLGLCYGANTFFHAAKAYIEG
YHTVPKGRCRQ
VVTGMAWLFFVSWGMFPILFILGPEGFGVLSVYGSTVGHTIIDLMSKNCWGLLGHYLRV
LIHEHILIHGD
IRKTTKLNIGGTEIEVETLVEDEAEAGAVP

FIG. 38J

ChR2 ChETA (E123A) [SEQ ID NO: 11]
MDYGGALSAVGRELLFVTNPVVVNGSVLVPEDQCYCAGWIESRGTNGAQTASNVLQWLA
AGFSILLLMFY
AYQTWKSTCGWEEIYVCAIEMVKVILEFFFEFKNPSMLYLATGHRVQWLRYAAWLLTCP
VILIHLSNLTG
LSNDYSRRTMGLLVSDIGTIVWGATSAMATGYVKVIFFCLGLCYGANTFFHAAKAYIEG
YHTVPKGRCRQ
VVTGMAWLFFVSWGMFPILFILGPEGFGVLSVYGSTVGHTIIDLMSKNCWGLLGHYLRV
LIHEHILIHGD
IRKTTKLNIGGTEIEVETLVEDEAEAGAVP

FIG. 38K

ChR2 ChETA (E123T) [SEQ ID NO: 12]
MDYGGALSAVGRELLFVTNPVVVNGSVLVPEDQCYCAGWIESRGTNGAQTASNVLQWLA
AGFSILLLMFY
AYQTWKSTCGWEEIYVCAIEMVKVILEFFFEFKNPSMLYLATGHRVQWLRYATWLLTCP
VILIHLSNLTG
LSNDYSRRTMGLLVSDIGTIVWGATSAMATGYVKVIFFCLGLCYGANTFFHAAKAYIEG
YHTVPKGRCRQ
VVTGMAWLFFVSWGMFPILFILGPEGFGVLSVYGSTVGHTIIDLMSKNCWGLLGHYLRV
LIHEHILIHGD
IRKTTKLNIGGTEIEVETLVEDEAEAGAVP

FIG. 38L

iC1C2 (protein) [SEQ ID NO: 51]
MSRRPWLLALALAVALAAGSAGASTGSDATVPVATQDGPDYVFHRAHERMLFQTSYT
LENNGSVICIPNNGQCFCLAWLKSNGTNAEKLAANILQWITFALSALCLMFYGYQTWKS
TCGWEEIYVATIEMIKFIIEYFHEFDEPAVIYSSNGNKTVWLRYAEWLLTCPVILIHLSNLT
GLANDYNKRTMGLLVSDIGTIVWGTTAALSKGYVRVIFFLMGLCYGIYTFFNAAKVYIEA
YHTVPKGRCRQVVTGMAWLFFVSWGMFPILFILGPEGFGVLSVYGSTVGHTIIDLMSK
NCWGLLGHYLRVLIHEHILIHGDIRKTTKLNIGGTEIEVETLVEDEAEAGAV

Figure 38M

ChrimsonR (protein) [SEQ ID NO: 52]
MAELISSATRSLFAAGGINPWPNPYHHEDMGCGGMTPTGECFSTEWWCDPSYGLSD
AGYGYCFVEATGGYLVVGVEKKQAWLHSRGTPGEKIGAQVCQWIAFSIAIALLTFYGF
SAWKATCGWEEVYVCCVEVLFVTLEIFKEFSSPATVYLSTGNHAYCLRYFEWLLSCPVI
LIRLSNLSGLKNDYSKRTMGLIVSCVGMIVFGMAAGLATDWLKWLLYIVSCIYGGYMYF
QAAKCYVEANHSVPKGHCRMVVKLMAYAYFASWGSYPILWAVGPEGLLKLSPYANSI
GHSICDIIAKEFWTFLAHHLRIKIHEHILIHGDIRKTTKMEIGGEEVEVEEFVEEEDEDTV

Figure 38N

SwiChR (protein): [SEQ ID NO: 53]
MSRRPWLLALALAVALAAGSAGASTGSDATVPVATQDGPDYVFHRAHERMLFQTSYTLENNGSVICIPNNG
QCFCLAWLKSNGTNAEKLAANILQWISFALSALCLMFYGYQTWKSTCGWEEIYVATISMIKFIIEYFHSFDEPA
VIYSSNGNKTKWLRYASWLLTTPVILIRLSNLTGLANDYNKRTMGLLVSDIGTIVWGTTAALSKGYVRVIFFLM
GLCYGIYTFFNAAKVYIEAYHTVPKGRCRQVVTGMAWLFFVSWGMFPILFILGPEGFGVLSKYGSNVGHTIID
LMSKQCWGLLGHYLRVLIHEHILIHGDIRKTTKLNIGGTEIEVETLVEDEAEAGAVSSEDLYFQ

Figure 38O

SwiChR2.0 (protein): [SEQ ID NO: 54]
MDYGGALSAVGLFQTSYTLENNGSVICIPNNGQCFCLAWLKSNGTNAEKLAANILQWISFALSALCLMFYGY
QTWKSTCGWEEIYVATISMIKFIIEYFHSFDEPAVIYSSNGNKTKWLRYASWLLTAPVILIRLSNLTGLANDYNK
RTMGLLVSDIGTIVWGTTAALSKGYVRVIFFLMGLCYGIYTFFNAAKVYIEAYHTVPKGRCRQVVTGMAWLF
FVSWGMFPILFILGPEGFGVLSKYGSNVGHTIIDLMSKQCWGLLGHYLRVLIHEHILIHGDIRKTTKLNIGGTEI
EVETLVEDEAEAGAV

Figure 38P

SwiChR3.0 (protein): [SEQ ID NO: 55]
MDYGGALSAVGLFQTSYTLENNGSVICIPNNGQCFCLAWLKSNGTNAEKLAANILQWISFALSALCLMFYGY
QTWKSTCGWENIYVATIQMIKFIIEYFHSFDEPAVIYSSNGNKTRWLRYASWLLTAPVILIHLSNLTGLANDYN
KRTMGLLVSDIGTIVWGTTAALSKGYVRVIFFLMGLCYGIYTFFNAAKVYIEAYHTVPKGRCRQVVTGMAWL
FFVSWGMFPILFILGPEGFGVLSRYGSNVGHTIIDLMSKQCWGLLGHYLRVLIHSHILIHGDIRKTTKLNIGGTEI
EVETLVEDEAEAGAV

Figure 38Q

iC1C2 2.0 (protein): [SEQ ID NO: 56]
MDYGGALSAVGLFQTSYTLENNGSVICIPNNGQCFCLAWLKSNGTNAEKLAANILQWISFALSALCLMFYGY
QTWKSTCGWEEIYVATISMIKFIIEYFHSFDEPAVIYSSNGNKTKWLRYASWLLTCPVILIRLSNLTGLANDYNK
RTMGLLVSDIGTIVWGTTAALSKGYVRVIFFLMGLCYGIYTFFNAAKVYIEAYHTVPKGRCRQVVTGMAWLF
FVSWGMFPILFILGPEGFGVLSKYGSNVGHTIIDLMSKQCWGLLGHYLRVLIHEHILIHGDIRKTTKLNIGGTEI
EVETLVEDEAEAGAV

Figure 38R

iC1C2 3.0 (protein): [SEQ ID NO: 57]
MDYGGALSAVGLFQTSYTLENNGSVICIPNNGQCFCLAWLKSNGTNAEKLAANILQWISFALSALCLMFYGY
QTWKSTCGWENIYVATIQMIKFIIEYFHSFDEPAVIYSSNGNKTRWLRYASWLLTCPVILIHLSNLTGLANDYN
KRTMGLLVSDIGTIVWGTTAALSKGYVRVIFFLMGLCYGIYTFFNAAKVYIEAYHTVPKGRCRQVVTGMAWL
FFVSWGMFPILFILGPEGFGVLSRYGSNVGHTIIDLMSKQCWGLLGHYLRVLIHSHILIHGDIRKTTKLNIGGTEI
EVETLVEDEAEAGAV

Figure 38S

C1V1 (splice variant 2) [gi|342356711|gb|AEL28924.1] [SEQ ID NO: 13]
MSRRPWLLALALAVALAAGSAGASTGSDATVPVATQDGPDYVFHRAHERMLFQTSYTLE
NNGSVICIPNN
GQCFCLAWLKSNGTNAEKLAANILQWITFALSALCLMFYGYQTWKSTCGWEEIYVATIE
MIKFIIEYFHE
FDEPAVIYSSNGNKTVWLRYAEWLLTCPVLLIHLSNLTGLKDDYSKRTMGLLVSDVGCI
VWGATSAMCTG
WTKILFFLISLSYGMYTYFHAAKVYIEAFHTVPKGICRELVRVMAWTFFVAWGMFPVLF
LLGTEGFGHIS
PYGSAIGHSILDLIAKNMWGVLGNYLRVKIHEHILLYGDIRKKQKITIAGQEMEVETLV
AEEED

FIG. 39A

C1V1 (splice variant 2) ChETA (E122T) [SEQ ID NO: 14]
MSRRPWLLALALAVALAAGSAGASTGSDATVPVATQDGPDYVFHRAHERMLFQTSYTLE
NNGSVICIPNN
GQCFCLAWLKSNGTNAEKLAANILQWITFALSALCLMFYGYQTWKSTCGWETIYVATIE
MIKFIIEYFHE
FDEPAVIYSSNGNKTVWLRYAEWLLTCPVLLIHLSNLTGLKDDYSKRTMGLLVSDVGCI
VWGATSAMCTG
WTKILFFLISLSYGMYTYFHAAKVYIEAFHTVPKGICRELVRVMAWTFFVAWGMFPVLF
LLGTEGFGHIS
PYGSAIGHSILDLIAKNMWGVLGNYLRVKIHEHILLYGDIRKKQKITIAGQEMEVETLV
AEEED

FIG. 39B

C1V1 (splice variant 2) ChETA (E162T) [SEQ ID NO: 15]
MSRRPWLLALALAVALAAGSAGASTGSDATVPVATQDGPDYVFHRAHERMLFQTSYTLE
NNGSVICIPNN
GQCFCLAWLKSNGTNAEKLAANILQWITFALSALCLMFYGYQTWKSTCGWEEIYVATIE
MIKFIIEYFHE
FDEPAVIYSSNGNKTVWLRYATWLLTCPVLLIHLSNLTGLKDDYSKRTMGLLVSDVGCI
VWGATSAMCTG
WTKILFFLISLSYGMYTYFHAAKVYIEAFHTVPKGICRELVRVMAWTFFVAWGMFPVLF
LLGTEGFGHIS
PYGSAIGHSILDLIAKNMWGVLGNYLRVKIHEHILLYGDIRKKQKITIAGQEMEVETLV
AEEED

FIG. 39C

C1V1 (splice variant 2) ChETA (E122T/E162T) [SEQ ID NO: 16]
MSRRPWLLALALAVALAAGSAGASTGSDATVPVATQDGPDYVFHRAHERMLFQTSYTLE
NNGSVICIPNN
GQCFCLAWLKSNGTNAEKLAANILQWITFALSALCLMFYGYQTWKSTCGWETIYVATIE
MIKFIIEYFHE
FDEPAVIYSSNGNKTVWLRYATWLLTCPVLLIHLSNLTGLKDDYSKRTMGLLVSDVGCI
VWGATSAMCTG
WTKILFFLISLSYGMYTYFHAAKVYIEAFHTVPKGICRELVRVMAWTFFVAWGMFPVLF
LLGTEGFGHIS
PYGSAIGHSILDLIAKNMWGVLGNYLRVKIHEHILLYGDIRKKQKITIAGQEMEVETLV
AEEED

FIG. 39D

C1V1 (splice variant 1) ChETA (E162T)
[gi|342356709|gb|AEL28923.1] [SEQ ID NO: 17]
MSRRPWLLALALAVALAAGSAGASTGSDATVPVATQDGPDY17VFHRAHERMLFQTSYT
LENNGSVICIPNN
GQCFCLAWLKSNGTNAEKLAANILQWITFALSALCLMFYGYQTWKSTCGWEEIYVATIE
MIKFIIEYFHE
FDEPATLWLSSGNGVVWMRYGTWLLTCPVLLIHLSNLTGLKDDYSKRTMGLLVSDIACI
VWGATSAMCTG
WTKILFFLISLSYGMYTYFHAAKVYIEAFHTVPKGICRELVRVMAWTFFVAWGMFPVLF
LLGTEGFGHIS
PYGSAIGHSILDLIAKNMWGVLGNYLRVKIHEHILLYGDIRKKQKITIAGQEMEVETLV
AEEEDDTVKQS
TAKYASR

FIG. 39E

C1V1 (splice variant 1) ChETA (E122T) [SEQ ID NO: 18]
MSRRPWLLALALAVALAAGSAGASTGSDATVPVATQDGPDYVFHRAHERMLFQTSYTLE
NNGSVICIPNN
GQCFCLAWLKSNGTNAEKLAANILQWITFALSALCLMFYGYQTWKSTCGWETIYVATIE
MIKFIIEYFHE
FDEPATLWLSSGNGVVWMRYGEWLLTCPVLLIHLSNLTGLKDDYSKRTMGLLVSDIACI
VWGATSAMCTG
WTKILFFLISLSYGMYTYFHAAKVYIEAFHTVPKGICRELVRVMAWTFFVAWGMFPVLF
LLGTEGFGHIS
PYGSAIGHSILDLIAKNMWGVLGNYLRVKIHEHILLYGDIRKKQKITIAGQEMEVETLV
AEEEDDTVKQSnphr
TAKYASR

FIG. 39F

C1V1 splice variant 1 ChETA (E122T/E162T) [SEQ ID NO: 19]
MSRRPWLLALALAVALAAGSAGASTGSDATVPVATQDGPDYVFHRAHERMLFQTSYTLE
NNGSVICIPNN
GQCFCLAWLKSNGTNAEKLAANILQWITFALSALCLMFYGYQTWKSTCGWETIYVATIE
MIKFIIEYFHE
FDEPATLWLSSGNGVVWMRYGTWLLTCPVLLIHLSNLTGLKDDYSKRTMGLLVSDIACI
VWGATSAMCTG
WTKILFFLISLSYGMYTYFHAAKVYIEAFHTVPKGICRELVRVMAWTFFVAWGMFPVLF
LLGTEGFGHIS
PYGSAIGHSILDLIAKNMWGVLGNYLRVKIHEHILLYGDIRKKQKITIAGQEMEVETLV
AEEEDDTVKQS
TAKYASR

FIG. 39G

C1V1 splice variant 1 [SEQ ID NO: 49]
MSRRPWLLALALAVALAAGSAGASTGSDATVPVATQDGPDYVFHRAHERMLFQTSYTLE
NNGSVICIPNN
GQCFCLAWLKSNGTNAEKLAANILQWITFALSALCLMFYGYQTWKSTCGWEEIYVATIE
MIKFIIEYFHE
FDEPATLWLSSGNGVVWMRYGEWLLTCPVLLIHLSNLTGLKDDYSKRTMGLLVSDIACI
VWGATSAMCTG
WTKILFFLISLSYGMYTYFHAAKVYIEAFHTVPKGICRELVRVMAWTFFVAWGMFPVLF
LLGTEGFGHIS
PYGSAIGHSILDLIAKNMWGVLGNYLRVKIHEHILLYGDIRKKQKITIAGQEMEVETLV
AEEEDDTVKQS
TAKYASR

FIG. 39H

VChR1 [gi|189015852|gb|ACD70142.1] [SEQ ID NO: 20]
MDYPVARSLIVRYPTDLGNGTVCMPRGQCYCEGWLRSRGTSIEKTIAITLQWVVFALSV
ACLGWYAYQAW
RATCGWEEVYVALIEMMKSIIEAFHEFDSPATLWLSSGNGVVWMRYGEWLLTCPVLLIH
LSNLTGLKDDY
SKRTMGLLVSDVGCIVWGATSAMCTGWTKILFFLISLSYGMYTYFHAAKVYIEAFHTVP
KGICRELVRVM
AWTFFVAWGMFPVLFLLGTEGFGHISPYGSAIGHSILDLIAKNMWGVLGNYLRVKIHEH
ILLYGDIRKKQ
KITIAGQEMEVETLVAEEED

FIG. 40A

VChR1 (C123S) [VSFO] [SEQ ID NO: 21]
MDYPVARSLIVRYPTDLGNGTVCMPRGQCYCEGWLRSRGTSIEKTIAITLQWVVFALSV
ACLGWYAYQAW
RATCGWEEVYVALIEMMKSIIEAFHEFDSPATLWLSSGNGVVWMRYGEWLLTSPVLLIH
LSNLTGLKDDY
SKRTMGLLVSDVGCIVWGATSAMCTGWTKILFFLISLSYGMYTYFHAAKVYIEAFHTVP
KGICRELVRVM
AWTFFVAWGMFPVLFLLGTEGFGHISPYGSAIGHSILDLIAKNMWGVLGNYLRVKIHEH
ILLYGDIRKKQ
KITIAGQEMEVETLVAEEED

FIG. 40B

VChR1 (C123S/D151A) (VSSFO) [SEQ ID NO: 22]
MDYPVARSLIVRYPTDLGNGTVCMPRGQCYCEGWLRSRGTSIEKTIAITLQWVVFALSV
ACLGWYAYQAW
RATCGWEEVYVALIEMMKSIIEAFHEFDSPATLWLSSGNGVVWMRYGEWLLTSPVLLIH
LSNLTGLKDDY
SKRTMGLLVSAVGCIVWGATSAMCTGWTKILFFLISLSYGMYTYFHAAKVYIEAFHTVP
KGICRELVRVM
AWTFFVAWGMFPVLFLLGTEGFGHISPYGSAIGHSILDLIAKNMWGVLGNYLRVKIHEH
ILLYGDIRKKQ
KITIAGQEMEVETLVAEEED

FIG. 40C

ReaChR [gi|530752655|gb|AGT48260.1] [SEQ ID NO: 23]
MVSRRPWLLALALAVALAAGSAGASTGSDATVPVATQDGPDYVFHRAHERMLFQTSYTL
ENNGSVICIPN
NGQCFCLAWLKSNGTNAEKLAANILQWVVFALSVACLGWYAYQAWRATCGWEEVYVALI
EMMKSIIEAFH
EFDSPATLWLSSGNGVVWMRYGEWLLTCPVILIHLSNLTGLKDDYSKRTMGLLVSDVGC
IVWGATSAMCT
GWTKILFFLISLSYGMYTYFHAAKVYIEAFHTVPKGLCRQLVRAMAWLFFVSWGMFPVL
FLLGPEGFGHI
SPYGSAIGHSILDLIAKNMWGVLGNYLRVKIHEHILLYGDIRKKQKITIAGQEMEVETL
VAEEEDKYESS

FIG. 41A

VCOMET [gi|530752657|gb|AGT48261.1] [SEQ ID NO:24]
MVSRRPWLLALALAVALAAGSAGASTGSDATVPVATQDGPDYVFHRAHERMLFQTSYTL
ENNGSVICIPN
NGQCFCLAWLKSNGTNAEKLAANILQWVVFALSVACLGWYAYQAWRATCGWEEVYVALI
EMMKSIIEAFH
EFDSPATLWLSSGNGVVWMRYGEWLLTCPVLLIHLSNLTGLKDDYSKRTMGLLVSDVGC
IVWGATSAMCT
GWTKILFFLISLSYGMYTYFHAAKVYIEAFHTVPKGLCRQLVRAMAWLFFVSWGMFPVL
FLLGPEGFGHI
SPYGSAIGHSILDLIAKNMWGVLGNYLRVKIHEHILLYGDIRKKQKITIAGQEMEVETL
VAEEEDKYESS

FIG. 41B

Arch [gi|282892261|gb|ADB03110.1 [SEQ ID NO:25]
MDPIALQAGYDLLGDGRPETLWLGIGTLLMLIGTFYFLVRGWGVTDKDAREYYAVTILV
PGIASAAYLSM
FFGIGLTEVTVGGEMLDIYYARYADWLFTTPLLLLDLALLAKVDRVTIGTLVGVDALMI
VTGLIGALSHT
AIARYSWWLFSTICMIVVLYFLATSLRSAAKERGPEVASTFNTLTALVLVLWTAYPILW
IIGTEGAGVVG
LGIETLLFMVLDVTAKVGFGFILLRSRAILGDTEAPEPSAGADVSAAD

FIG. 42A

ArchT [gi 328672376|gb|AEB26832.1] [SEQ ID NO:26]
MDPIALQAGYDLLGDGRPETLWLGIGTLLMLIGTFYFIVKGWGVTDKEAREYYSITILV
PGIASAAYLSM
FFGIGLTEVTVAGEVLDIYYARYADWLFTTPLLLLDLALLAKVDRVSIGTLVGVDALMI
VTGLIGALSHT
PLARYSWWLFSTICMIVVLYFLATSLRAAAKERGPEVASTFNTLTALVLVLWTAYPILW
IIGTEGAGVVG
LGIETLLFMVLDVTAKVGFGFILLRSRAILGDTEAPEP

FIG. 42B

eArch3.0-EYFP [SEQ ID NO: 24 from published PCT application from Published PCT application WO/2013/126521] [SEQ ID NO: 27]
MDPIALQAGYDLLGDGRPETLWLGIGTLLMLIGTFYFLVRGWGVTDKDAREYYAVTILV
PGIASA
AYLSMFFGIGLTEVTVGGEMLDIYYARYADWLFTTPLLLLDLALLAKVDRVTIGTLVGV
DALMIV
TGLIGALSHTAIARYSWWLFSTICMIVVLYFLATSLRSAAKERGPEVASTFNTLTALVL
VLWTAYP
ILWIIGTEGAGVVGLGIETLLFMVLDVTAKVGFGFILLRSRAILGDTEAPEPSAGADVS
AADRPVV
AVSKAAAKSRITSEGEYIPLDQIDINVVSKGEELFTGVVPILVELDGDVNGHKFSVSGE
GEGDATY
GKLTLKFICTTGKLPVPWPTLVTTFGYGLQCFARYPDHMKQHDFFKSAMPEGYVQERTI
FFKDDG
NYKTRAEVKFEGDTLVNRIELKGIDFKEDGNILGHKLEYNYNSHNVYIMADKQKNGIKV
NFKIRH
NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSYQSALSKDPNEKRDHMVLLEFVTAAG
ITLGM DELYKFCYENEV

FIG. 42C

Arch 3.0 (protein) [SEQ ID NO: 58]

MDPIALQAGYDLLGDGRPETLWLGIGTLLMLIGTFYFLVRGWGVTDKDAREYYAVTILV
PGIASAAYLSMFFGIGLTEVTVGGEMLDIYYARYADWLFTTPLLLLDLALLAKVDRVTIG
TLVGVDALMIVTGLIGALSHTAIARYSWWLFSTICMIVVLYFLATSLRSAAKERGPEVAS
TFNTLTALVLVLWTAYPILWIIGTEGAGVVGLGIETLLFMVLDVTAKVGFGFILLRSRAIL
GDTEAPEPSAGADVSAADRPVVAVSKAAAKSRITSEGEYIPLDQIDINVFCYENEV

Figure 42D

ArchT 3.0 (protein) [SEQ ID NO: 59]

MDPIALQAGYDLLGDGRPETLWLGIGTLLMLIGTFYFIVKGWGVTDKEAREYYSITILVP
GIASAAYLSMFFGIGLTEVTVAGEVLDIYYARYADWLFTTPLLLLDLALLAKVDRVSIGT
LVGVDALMIVTGLIGALSHTPLARYSWWLFSTICMIVVLYFLATSLRAAAKERGPEVAST
FNTLTALVLVLWTAYPILWIIGTEGAGVVGLGIETLLFMVLDVTAKVGFGFILLRSRAIL
GDTEAPEP

Figure 42E

Mac [gi|282892265|gb|ADB03112.1] [SEQ ID NO:28]
MIVDQFEEVLMKTSQLFPLPTATQSAQPTHVAPVPTVLPDTPIYETVGDSGSKTLWVVF
VLMLIASAAFT
ALSWKIPVNRRLYHVITTIITLTAALSYFAMATGHGVALNKIVIRTQHDHVPDTYETVY
RQVYYARYIDW
AITTPLLLLDLGLLAGMSGAHIFMAIVADLIMVLTGLFAAFGSEGTPQKWGWYTIACIA
YIFVVWHLVLN
GGANARVKGEKLRSFFVAIGAYTLILWTAYPIVWGLADGARKIGVDGEIIAYAVLDVLA
KGVFGAWLLVT
HANLRESDVELNGFWANGLNREGAIRIGEDDGA

FIG. 43

BR [Published US patent application 20130019325] [SEQ ID NO: 29]
MLELLPTAVEGVSQAQITGRPEWIWLALGTALMGLGTLYFLVKGMGVSDPDAKKFYAIT
TLVPAIAFTMYLSMLLGYGLT
MVPFGGEQNPIYWARYADWLFTTPLLLLDLALLVDADQGTILALVGADGIMIGTGLVGA
LTKVYSYRFVWWAISTAAMLY
ILYVLFFGFTSKAESMRPEVASTFKVLRNVTVVLWSAYPVVWLIGSEGAGIVPLNIETL
LFMVLDVSAKVGFGLILLRSR
AIFGEAEAPEPSAGDGAAATSD

FIG. 44

DChR1 [gi|373427779|gb|AEY68833.1] [SEQ ID NO: 30]
MRRRESQLAYLCLFVLIAGWAPRLTESAPDLAERRPPSERNTPYANIKKVPNITEPNAN
VQLDGWALYQD
FYYLAGSDKEWVVGPSDQCYCRAWSKSHGTDREGEAAVVWAYIVFAICIVQLVYFMFAA
WKATVGWEEVY
VNIIELVHIALVIWVEFDKPAMLYLNDGQMVPWLRYSAWLLSCPVILIHLSNLTGLKGD
YSKRTMGLLVS
DIGTIVFGTSAALAPPNHVKVILFTIGLLYGLFTFFTAAKVYIEAYHTVPKGQCRNLVR
AMAWTYFVSWA
MFPILFILGREGFGHITYFGSSIGHFILEIFSKNLWSLLGHGLRYRIRQHIIIHGNLTK
KNKINIAGDNV
EVEEYVDSNDKDSDV

FIG. 45A

GtR3 [gi|373427781|gb|AEY68834.1] [SEQ ID NO: 31]
MDYGGALSAVGRELLFVTNPVVVNGSVLVPEDQCYCAGWIESRGTNGASSFGKALLEFV
FIVFACITLLL
GINAAKSKAASRVLFPATFVTGIASIAYFSMASGGGWVIAPDCRQLFVARYLDWLITTP
LLLIDLGLVAG
VSRWDIMALCLSDVLMIATGAFGSLTVGNVKWVWWFFGMCWFLHIIFALGKSWAEAAKA
KGGDSASVYSK
IAGITVITWFCYPVVWVFAEGFGNFSVTFEVLIYGVLDVISKAVFGLILMSGAATGYES
I

FIG. 45B

NpHR [gi|134153992|gb|AB064387.1] [SEQ ID NO: 32]
MTETLPPVTESAVALQAEVTQRELFEFVLNDPLLASSLYINIALAGLSILLFVFMTRGL
DDPRAKLIAVS
TILVPVVSIASYTGLASGLTISVLEMPAGHFAEGSSVMLGGEEVDGVVTMWGRYLTWAL
STPMILLALGL
LAGSNATKLFTAITFDIAMCVTGLAAALTTSSHLMRWFWYAISCACFLVVLYILLVEWA
QDAKAAGTADM
FNTLKLLTVVMWLGYPIVWALGVEGIAVLPVGVTSWGYSFLDIVAKYIFAFLLLNYLTS
NESVVSGSILD
VPSASGTPADD

FIG. 46A

eYFP-NpHR3.0 [SEQ ID NO: 2 from Published PCT application
WO/2013/126521] [SEQ ID NO: 33]
MTETLPPVTESAVALQAEVTQRELFEFVLNDPLLASSLYINIALAGLSILLFVFMTRGL
DDPRAKLIAV
STILVPVVSIASYTGLASGLTISVLEMPAGHFAEGSSVMLGGEEVDGVVTMWGRYLTWA
LSTPMILL
ALGLLAGSNATKLFTAITFDIAMCVTGLAAALTTSSHLMRWFWYAISCACFLVVLYILL
VEWAQDA
KAAGTADMFNTLKLLTVVMWLGYPIVWALGVEGIAVLPVGVTSWGYSFLDIVAKYIFAF
LLLNYLT
SNESVVSGSILDVPSASGTPADDAAAKSRITSEGEYIPLDQIDINVVSKGEELFTGVVP
ILVELDGDVN
GHKFSVSGEGEGDATYGKLTLKFICTTGKLPVPWPTLVTTFGYGLQCFARYPDHMKQHD
FFKSAMP
EGYVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNILGHKLEYNYNSH
NVYIMAD
KQKNGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSYQSALSKDPNEK
RDHMVLL EFVTAAGITLGMDELYKFCYENEV

FIG. 46B

eYFP-NpHR3.1 [SEQ ID NO: 3 from Published PCT application WO/2013/126521] [SEQ ID NO: 34]
MVTQRELFEFVLNDPLLASSLYINIALAGLSILLFVFMTRGLDDPRAKLIAVSTILVPV
VSIASYTGLA
SGLTISVLEMPAGHFAEGSSVMLGGEEVDGVVTMWGRYLTWALSTPMILLALGLLAGSN
ATKLFT
AITFDIAMCVTGLAAALTTSSHLMRWFWYAISCACFLVVLYILLVEWAQDAKAAGTADM
FNTLKL
LTVVMWLGYPIVWALGVEGIAVLPVGVTSWGYSFLDIVAKYIFAFLLLNYLTSNESVVS
GSILDVPS
ASGTPADDAAAKSRITSEGEYIPLDQIDINVVSKGEELFTGVVPILVELDGDVNGHKFS
VSGEGEGDA
TYGKLTLKFICTTGKLPVPWPTLVTTFGYGLQCFARYPDHMKQHDFFKSAMPEGYVQER
TIFFKDD
GNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNILGHKLEYNYNSHNVYIMADKQKNGIK
VNFKIRH
NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSYQSALSKDPNEKRDHMVLLEFVTAAG
ITLGMDE LYKFCYENEV

FIG. 46C

Optoβ2AR [Published US patent application 20110112179] [SEQ ID NO: 35]
MNGTEGPNFYVPFSNKTGVVRSPFEAPQYYLAEPWQFSMLAAYMFLLIMLGFPINFLTL
YVIAKFERLQTVLNYILLNLA
VADLFMVFGGFTTTLYTSLHGYFVFGPTGCNLEGFFATLGGEIALWSLVVLAIERYVVV
TSPFKYQSLLTKNKAIMGVAF
TWVMALACAAPPLVGWSRYIPEGMQCSCGIDYYTPHEETNNESFVIYMFVVHFIIPLIV
IFFCYGRVFQVAKRQLQKIDK
SEGRFHSPNLGQVEQDGRSGHGLRRSSKFCLKEHKALRMVIIMVIAFLICWLPYAGVAF
YIFTHQGSDFGPIFMTIPAFF
AKTSAVYNPVIYIMMNKQFRIAFQELLCLRRSSSKAYGNGYSSNSNGKTDYMGEASGCQ
LGQEKESERLCEDPPGTESFV
NCQGTVPSLSLDSQGRNCSTNDSPLTETSQVAPA

FIG. 47A

Optoα1AR [Published US patent application 20110112179] [SEQ ID NO: 36]
MNGTEGPNFYVPFSNKTGVVRSPFEAPQYYLAEPWQFSMLAAYMFLLIMLGFPINFLTL
YVVACHRHLHSVLNYILLNLA
VADLFMVFGGFTTTLYTSLHGYFVFGPTGCNLEGFFATLGGEIALWSLVVLAIERYVVV
SYPLRYPTIVTQRRAIMGVAF
TWVMALACAAPPLVGWSRYIPEGMQCSCGIDYYTPHEETNNESFVIYMFVVHFIIPLIV
IFFCYGRVYVVAKRESRGLKS
GLKTDKSDSEQVTLRIHRKNAPAGGSGMASAKTKTHFSVRLLKFSREKKAARMVIIMVI
AFLICWLPYAGVAFYIFTHQG
SDFGPIFMTIPAFFAKTSAVYNPVIYIMMNKQFRKAFQNVLRIQCLCRKQSSKHALGYT
LHPPSQAVEGQHKDMVRIPVG
SRETFYRISKTDGVCEWKFFSSMPRGSARITVSKDQSSCTTARVRSKSFLQVCCCVGPS
TPSLDKNHQVPTIKVHTISLS
ENGEEVTETSQVAPA

FIG. 47B

Trafficking sequence of human inward rectifier potassium channel Kir2.1 [SEQ ID NO: 12 from Published PCT application WO/2013/126521] [SEQ ID NO: 37]
KSRITSEGEYIPLDQIDINV

FIG. 48A

Signal peptide of hChR2 [SEQ ID NO: 13 from Published PCT application WO/2013/126521] [SEQ ID NO: 38]
MDYGGALSAVGRELLFVTNPVVVNGS

FIG. 48B

β2 subunit signal peptide of the neuronal nicotinic acetylcholine receptor [SEQ ID NO: 14 from Published PCT application WO/2013/126521] [SEQ ID NO: 39]
MAGHSNSMALFSFSLLWLCSGVLGTEF

FIG. 48C

Nicotinic acetylcholine receptor signal sequence [SEQ ID NO: 15 from Published PCT application WO/2013/126521] [SEQ ID NO: 40]
MGLRALMLWLLAAAGLVRESLQG

FIG. 48D

Nicotinic acetylcholine receptor signal sequence [SEQ ID NO: 16 from Published PCT application WO/2013/126521] [SEQ ID NO: 41]
MRGTPLLLVVSLFSLLQD

FIG. 48E

Endoplasmic reticulum (ER) export sequence [Published PCT application WO/2013/126521] [SEQ ID NO: 42]
VXXSL (where X is any amino acid)

FIG. 48F

Endoplasmic reticulum (ER) export sequence [SEQ ID NO: 17 from Published PCT application WO/2013/126521] [SEQ ID NO: 43]
VKESL

FIG. 48G

Endoplasmic reticulum (ER) export sequence [SEQ ID NO: 18 from Published PCT application WO/2013/126521] [SEQ ID NO: 44]
VLGSL

FIG. 48H

Endoplasmic reticulum (ER) export sequence [SEQ ID NO: 19 from Published PCT application WO/2013/126521] [SEQ ID NO: 45]
NANSFCYENEVALTSK

FIG. 48I

Endoplasmic reticulum (ER) export sequences [SEQ ID NO: 20 from Published PCT application WO/2013/126521] [SEQ ID NO: 46]
FXYENE (where X is any amino acid)

FIG. 48J

Endoplasmic reticulum (ER) export sequence [SEQ ID NO: 21 from Published PCT application WO/2013/126521] [SEQ ID NO: 47]
FCYENEV

FIG. 48K

Signal peptide [SEQ ID NO: 22 from Published PCT application WO/2013/126521] [SEQ ID NO: 48]
MTETLPPVTESAVALQAE

FIG. 48L

Polynucleotide encoding Champ [SEQ ID NO: 50]
cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgt
cgggcgacctttggtcgcccg
gcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttc
ctgcggccgcacgcgtgtgtc
tagactgcagagggccctgcgtatgagtgcaagtgggttttaggaccaggatgaggcgg
ggtgggggtgcctacctgacg
accgaccccgacccactggacaagcacccaaccccccattccccaaattgcgcatcccct
atcagagagggggagggggaaa
caggatgcggcgaggcgcgtgcgcactgccagcttcagcaccgcggacagtgccttcgc
ccccgcctggcggcgcgcgcc
accgccgcctcagcactgaaggcgcgctgacgtcactcgccggtcccccgcaaactccc
cttcccggccaccttggtcgc
gtccgcgccgccgccggcccagccggaccgcaccacgcgaggcgcgagataggggggca
cgggcgcgaccatctgcgctg
cggcgccggcgactcagcgctgcctcagtctgcggtgggcagcggaggagtcgtgtcgt
gcctgagagcgcagtcgagaa
ggtaccggatccgccaccatggaccccatcgctctgcaggctggttacgacctgctggg
tgacggcagacctgaaactct
gtggctgggcatcggcactctgctgatgctgattggaaccttctactttctggtccgcg
gatggggagtcaccgataagg
atgcccgggaatattacgctgtgactatcctggtgcccggaatcgcatccgccgcatat
ctgtctatgttctttggtatc
gggcttactgaggtgaccgtcgggggcgaaatgttggatatctattatgccaggtacgc
cgactggctgtttaccacccc
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tggtgggtgtggacgccctga
tgatcgtcactggcctcatcggagccttgagccacacggccatagccagatacagttgg
tggttgttctctacaatttgc
atgatagtggtgctctattttctggctacatccctgcgatctgctgcaaaggagcgggg
ccccgaggtggcatctacctt

FIG. 48M-1

taacaccctgacagctctggtcttggtgctgtggaccgcttaccctatcctgtggatca
taggcactgagggcgctggcg
tggtgggcctgggcatcgaaactctgctgtttatggtgttggacgtgactgccaaggtc
ggctttggctttatcctgttg
agatcccgggctattctgggcgacaccgaggcaccagaacccagtgccggtgccgatgt
cagtgccgccgacaagagcag
gatcaccagcgagggcgagtacatccccctggaccagatcgacatcaacgtgggcgcgc
ccggctccggagccacgaact
tctctctgttaaagcaagcaggagacgtggaagaaaaccccggtcccatggacctgaag
gagtcaccaagcgagggatca
ctgcagccatcaagcattcagattttcgctaatacaagcacactgcacggcatccggca
tatcttcgtgtacggcccact
gaccattcggagagtcctgtgggcagtggcctttgtcggaagcctgggactgctgctgg
tggagagctccgaaagagtca
gttactatttctcatatcagcacgtgactaaggtggacgaggtggtcgctcagtccctg
gtgtttcccgcagtcaccctg
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agagctgctggctctgctgga
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ggcagaaggccaacttcaaac
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aagttcaaaggccaggagtgtgggcatcaggacttcactaccgtgtttacaaagtacgg
caaatgttacatgttcaactc
cggggaagatggaaaacctctgctgacaactgtgaagggcgggacagggaatggactgg
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aaggtccagatccactcacag
agcgagccccctttcattcaggaactgggatttggagtggcaccaggattccagacatt
tgtcgctactcaggagcagcg
cctgacctatctgccacccccttggggcgagtgccgatctagtgaaatggggctggact
tctttcctgtgtactctatca

FIG. 48M CONTINUED

ccgcctgccgaattgattgtgagacacggtatatcgtggaaaactgcaattgtaggatg
gtccacatgcctggcgacgcc
ccattctgcactcccgaacagcataaagagtgtgctgaacctgcactggggctgctggc
tgagaaggatagtaactactg
cctgtgtagaacaccctgtaacctgactaggtataataaggaactgagcatggtgaaga
tcccttccaaaacatctgcaa
agtacctggagaagaagttcaacaagtctgagaagtacatcagtgaaaacattctggtg
ctggacatcttctttgaagct
ctgaattacgagaccattgaacagaagaaagcatatgaggtggccgctctgctggggga
tattggaggccagatgggact
gttcatcggcgccagcctgctgacaattctggagctgtttgactacatctatgagctga
ttaaggaaaaactgctggatc
tgctggggaaggaggaagaggaaggatcacacgacgaaaacatgagcacttgcgatacc
atgcctaatcacagcgagacc
atctcccatacagtgaatgtcccactgcagactgcactgggcaccctggaggaaattgc
ctgtgcggccgccaagagcag
gatcaccagcgagggcgagtacatccccctggaccagatcgacatcaacgtggtgagca
agggcgaggagctgttcaccg
gggtggtgcccatcctggtcgagctggacggcgacgtaaacggccacaagttcagcgtg
tccggcgagggcgagggcgat
gccacctacggcaagctgaccctgaagttcatctgcaccaccggcaagctgcccgtgcc
ctggcccaccctcgtgaccac
cttcggctacggcctgcagtgcttcgcccgctaccccgaccacatgaagcagcacgact
tcttcaagtccgccatgcccg
aaggctacgtccaggagcgcaccatcttcttcaaggacgacggcaactacaagacccgc
gccgaggtgaagttcgagggc
gacaccctggtgaaccgcatcgagctgaagggcatcgacttcagggaggacggcaacat
cctggggcacaagctggagta
caactacaacagccacaacgtctatatcatggccgacaagcagaagaacggcatcaagg
tgaacttcaagatccgccaca
acatcgaggacggcagcgtgcagctcgccgaccactaccagcagaacacccccatcggc
gacggccccgtgctgctgccc

FIG. 48M CONTINUED

gacaaccactacctgagctaccagtccgccctgagcaaagaccccaacgagaagcgcga
tcacatggtcctgctggagtt
cgtgaccgccgccgggatcactctcggcatggacgagctgtacaagttctgctacgaga
acgaggtgtaatgagaattcg
atatcaagcttatcgataatcaacctctggattacaaaatttgtgaaagattgactggt
attcttaactatgttgctcct
tttacgctatgtggatacgctgctttaatgcctttgtatcatgctattgcttcccgtat
ggctttcattttctcctcctt
gtataaatcctggttgctgtctctttatgaggagttgtggcccgttgtcaggcaacgtg
gcgtggtgtgcactgtgtttg
ctgacgcaacccccactggttggggcattgccaccacctgtcagctcctttccgggact
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gccacggcggaactcatcgccgcctgccttgcccgctgctggacaggggctcggctgtt
gggcactgacaattccgtggt
gttgtcggggaaatcatcgtcctttccttggctgctcgcctgtgttgccacctggattc
tgcgcgggacgtccttctgct
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gcagtggcacaatcttggctc
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caggctcagctaatttttgtttttttggtagagacggggtttcaccatattggccaggc
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cccttccctgtccttctgatt

FIG. 48M CONTINUED

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ctcagtgagcgagcgagcgcg
cagctgcctgcaggggcgcctgatgcggtattttctccttacgcatctgtgcggtattt
cacaccgcatacgtcaaagca
accatagtacgcgccctgtagcggcgcattaagcgcggcgggtgtggtggttacgcgca
gcgtgaccgctacacttgcca
gcgccctagcgcccgctcctttcgctttcttcccttcctttctcgccacgttcgccggc
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cgggggctcccttagggttccgatttagtgctttacggcacctcgaccccaaaaaact
tgatttgggtgatggttcacg
tagtgggccatcgccctgatagacggtttttcgccctttgacgttggagtccacgttct
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aaactggaacaacactcaaccctatctcgggctattcttttgatttataagggatttg
ccgatttcggcctattggtta
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acgcgccctgacgggcttgtc
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aaacgcgcgagacgaaagggcctcgtgatacgcctatttttataggttaatgtcatgat
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aggtggcacttttcggggaaatgtgcgcggaacccctatttgtttatttttctaaatac
attcaaatatgtatccgctca
tgagacaataaccctgataaatgcttcaataatattgaaaaaggaagagtatgagtatt
caacatttccgtgtcgcccttt
attcccttttttgcggcattttgccttcctgtttttgctcacccagaaacgctggtgaa
agtaaaagatgctgaagatca
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gttttcgccccgaagaacgtt

FIG. 48M CONTINUED

ttccaatgatgagcacttttaaagttctgctatgtggcgcggtattatcccgtattgac
gccgggcaagagcaactcggt
cgccgcatacactattctcagaatgacttggttgagtactcaccagtcacagaaaagca
tcttacggatggcatgacagt
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tgacaacgatcggaggaccga
aggagctaaccgcttttttgcacaacatgggggatcatgtaactcgccttgatcgttgg
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tactctagcttcccggcaacaattaatagactggatggaggcggataaagttgcaggac
cacttctgcgctcggcccttc
cggctggctggtttattgctgataaatctggagccggtgagcgtgggtctcgcggtatc
attgcagcactggggccagat
ggtaagccctcccgtatcgtagttatctacacgacggggagtcaggcaactatggatga
acgaaatagacagatcgctga
gataggtgcctcactgattaagcattggtaactgtcagaccaagtttactcatatatac
tttagattgatttaaaacttc
atttttaatttaaaaggatctaggtgaagatccttttttgataatctcatgaccaaaatc
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cactgagcgtcagaccccgtagaaaagatcaaaggatcttcttgagatccttttttttct
gcgcgtaatctgctgcttgca
aacaaaaaaaaccaccgctaccagcggtggtttgtttgccggatcaagagctaccaactc
tttttccgaaggtaactggct
tcagcagagcgcagataccaaatactgtccttctagtgtagccgtagttaggccaccac
ttcaagaactctgtagcaccg
cctacatacctcgctctgctaatcctgttaccagtggctgctgccagtggcgataagtc
gtgtcttaccgggttggactc
aagacgatagttaccggataaggcgcagcggtcgggctgaacgggggttcgtgcacac
agcccagcttggagcgaacga
cctacaccgaactgagatacctacagcgtgagctatgagaaagcgccacgcttcccgaa
gggagaaaggcggacaggtat

FIG. 48M CONTINUED

```
ccggtaagcggcagggtcggaacaggagagcgcacgagggagcttccagggggaaacgc
ctggtatctttatagtcctgt
cgggtttcgccacctctgacttgagcgtcgattttgtgatgctcgtcaggggggcgga
gcctatggaaaaacgccagca
acgcggccttttacggttcctggccttttgctggccttttgctcacatgt
```

FIG. 48M CONTINUED

CaMKiia (nucleotide): [SEQ ID NO: 60]
TTAACATTATGGCCTTAGGTCACTTCATCTCCATGGGGTTCTTCTTCTGATTTTCTAGAAAATGAGATGGG
GGTGCAGAGAGCTTCCTCAGTGACCTGCCCAGGGTCACATCAGAAATGTCAGAGCTAGAACTTGAACTC
AGATTACTAATCTTAAATTCCATGCCTTGGGGGCATGCAAGTACGATATACAGAAGGAGTGAACTCATT
AGGGCAGATGACCAATGAGTTTAGGAAAGAAGAGTCCAGGGCAGGGTACATCTACACCACCCGCCCAG
CCCTGGGTGAGTCCAGCCACGTTCACCTCATTATAGTTGCCTCTCTCCAGTCCTACCTTGACGGGAAGCA
CAAGCAGAAACTGGGACAGGAGCCCCAGGAGACCAAATCTTCATGGTCCCTCTGGGAGGATGGGTGGG
GAGAGCTGTGGCAGAGGCCTCAGGAGGGGCCCTGCTGCTCAGTGGTGACAGATAGGGGTGAGAAAGC
AGACAGAGTCATTCCGTCAGCATTCTGGGTCTGTTTGGTACTTCTTCTCACGCTAAGGTGGCGGTGTGAT
ATGCACAATGGCTAAAAAGCAGGGAGAGCTGGAAAGAAACAAGGACAGAGACAGAGGCCAAGTCAAC
CAGACCAATTCCCAGAGGAAGCAAAGAAACCATTACAGAGACTACAAGGGGGAAGGGAAGGAGAGAT
GAATTAGCTTCCCCTGTAAACCTTAGAACCCAGCTGTTGCCAGGGCAACGGGGCAATACCTGTCTCTTCA
GAGGAGATGAAGTTGCCAGGGTAACTACATCCTGTCTTTCTCAAGGACCATCCCAGAATGTGGCACCCA
CTAGCCGTTACCATAGCAACTGCCTCTTTGCCCCACTTAATCCCATCCCGTCTGTTAAAAGGGCCCTATAG
TTGGAGGTGGGGGAGGTAGGAAGAGCGATGATCACTTGTGGACTAAGTTTGTTCGCATCCCCTTCTCCA
ACCCCCTCAGTACATCACCCTGGGGGAACAGGGTCCACTTGCTCCTGGGCCCACACAGTCCTGCAGTATT
GTGTATATAAGGCCAGGGCAAAGAGGAGCAGGTTTTAAAGTGAAAGGCAGGCAGGTGTTGGGGAGGC
AGTTACCGGGGCAACGGGAACAGGGCGTTTCGGAGGTGGTTGCCATGGGGACCTGGATGCTGACGAA
GGCTCGCGAGGCTGTGAGCAGCCACAGTGCCCTGCTCAGAAGCCCCAAGCTCGTCAGTCAAGCCGGTTC
TCCGTTTGCACTCAGGAGCACGGGCAGGCGAGTGGCCCCTAGTTCTGGGGGCAGC

Figure 48N

ChEF [synthetic construct]: VERSION AHA49646.1 GI:558025409 [SEQ ID NO: 61]
mvsrrpwlla lalavalaag sagastgsda tvpvatqdgp dyvfhraher mlfqtsytle
nngsvicipn ngqcfclawl ksngtnaekl aanilqwitf alsalclmfy gyqtwkstcg
weeiyvatie mikfiieyfh efdepaviys sngnktvwlr yaewlltcpv ilihlsnltg
landynkrtm gllvsdigti vwgttaalsk gyvrvifflm glcygiytff naakvyieay
htvpkgrcrq vvtgmawlff vswgmfpilf ilgpegfgvl svygstvght iidlmskncw
gllghylrvl ihehililhgd irkttklnig gteievetlv edeaeagavn kgtgkyess

Figure 48O

Chronos [synthetic construct]: VERSION AHH02106.1 GI:575827602 [SEQ ID NO: 62]
metaatmtha fisavpsaea tirgllsaaa vvtpaadahg etsnattaga dhgcfphinh
gtelqhkiav glqwftviva ivqlifygwh sfkattgwee vyvcvielvk cfielfhevd
spatvyqtng gaviwlrysm wlltcpvili hlsnltglhe eyskrtmtil vtdignivwg
itaaftkgpl kilffmiglf ygvtcffqia kvyiesyhtl pkgvcrkick imayvffcsw
lmfpvmfiag heglglitpy tsgighlild liskntwgfl ghhlrvkihe hilihgdirk
tttinvagen meietfvdee eeggv

Figure 48P

Jaws [synthetic construct]: VERSION AID59893.1 GI:658355918 [SEQ ID NO: 63]
mtavsttatt vlqatqsdvl qeiqsnflln ssiwvniala gvvillfvam grdlesprak
liwvatmlvp lvsissyagl asgltvgflq mppghalagq evlspwgryl twtfstpmil
lalglladtd iaslftaitm digmcvtgla aalitsshll rwvfygisca ffvavlyvll
vqwpadaeaa gtseifgtlr iltvvlwlgy pilfalgseg vallsvgvts wgysgldila
kyvfafllir wvaanegtvs gsgmgigsgg aapadd

Figure 48Q

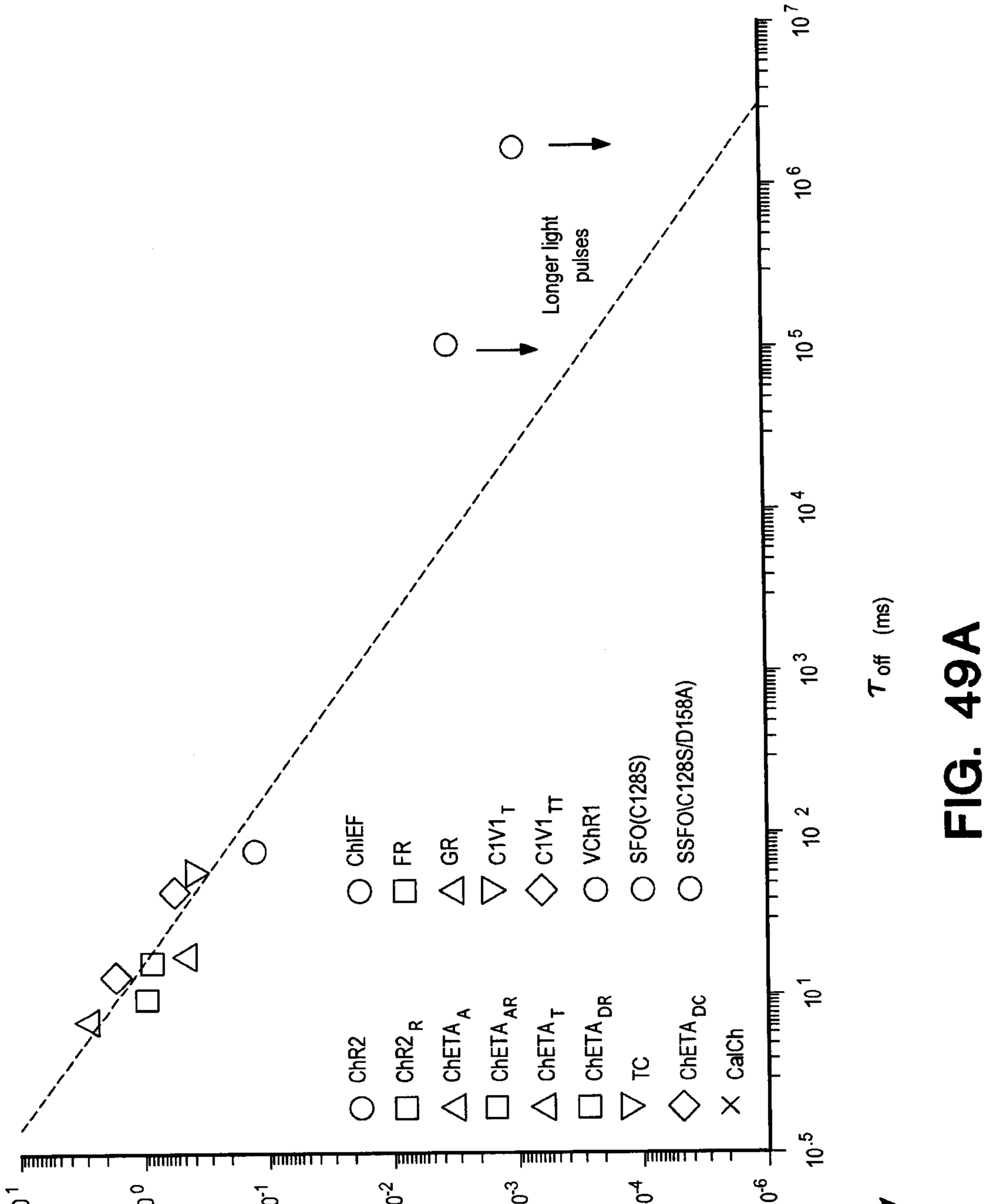

Longer light pulses
ChIEF
FR
GR
C1V1 T
C1V1 TT
VChR1
SFO(C128S)
SSFO\C128S/D158A)
ChR2
ChR2 R
ChETA A
ChETA AR
ChETA T
ChETA DR
TC
ChETA DC
CalCh
EPD 50 (mW mm-2)
τ off (ms)
252

FIG. 49A

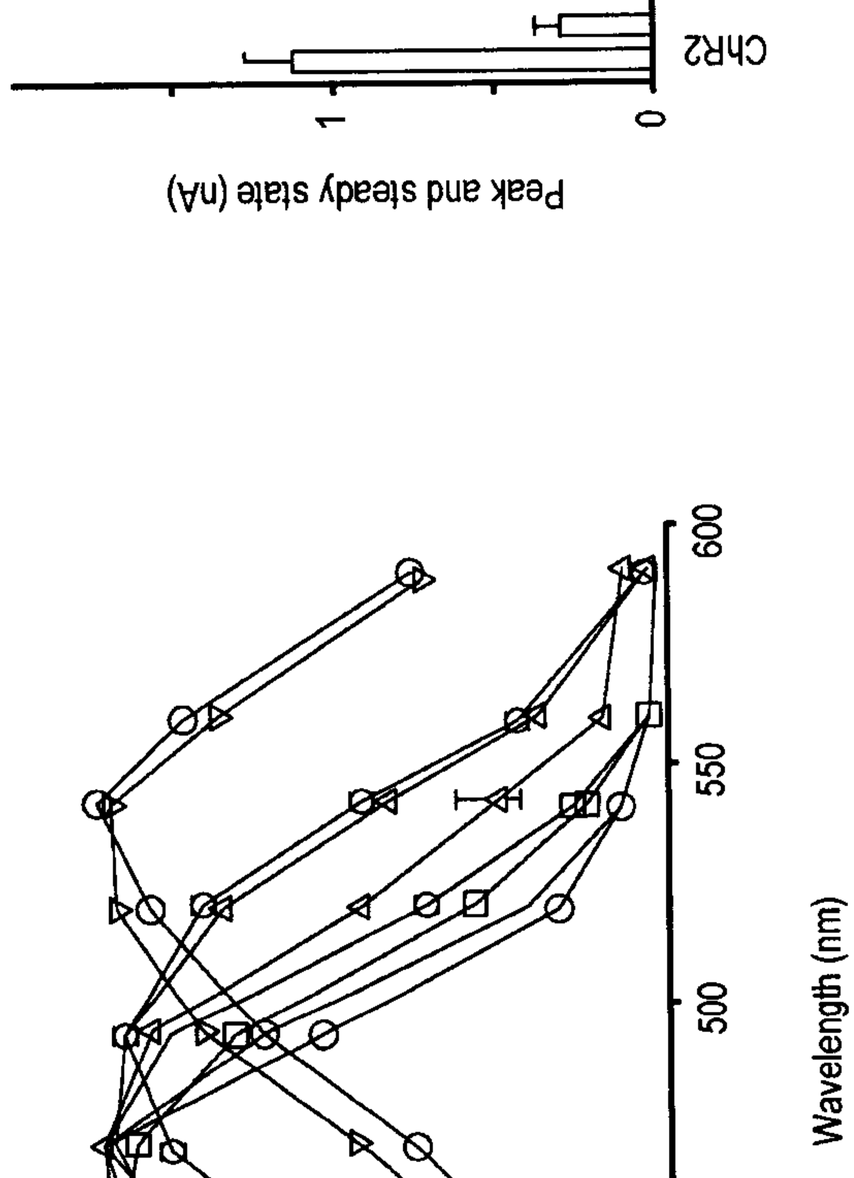


FIG. 49C

FIG. 49B

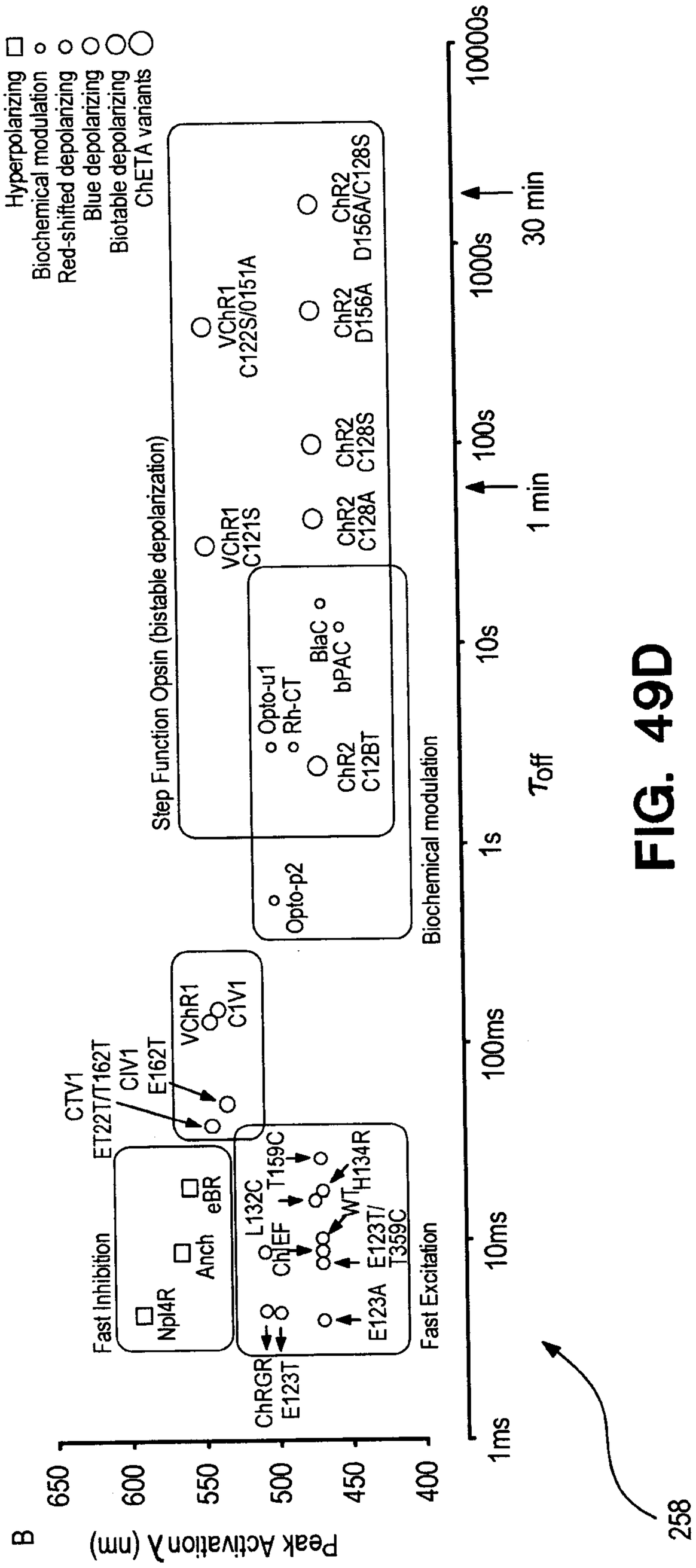

Peak Activation λ (nm)
650
600
550
500
450
400
B
Fast Inhibition
Npl4R
Anch
eBR
ChRGR
E123T
Fast Excitation
L132C
ChIEF
T159C
WT
H134R
E123T/
T359C
CTV1
ET22T/T162T
CIV1
E162T
VChR1
C1V1
1ms
10ms
100ms
1s
Toff
Biochemical modulation
Opto-p2
Step Function Opsin (bistable depolarization)
Opto-u1
Rh-CT
ChR2
C12BT
BlaC
bPAC
VChR1
C121S
ChR2
C128A
ChR2
C128S
VChR1
C122S/0151A
ChR2
D156A
ChR2
D156A/C128S
10s
100s
1000s
1 min
30 min
10000s
Hyperpolarizing
Biochemical modulation
Red-shifted depolarizing
Blue depolarizing
Biotable depolarizing
ChETA variants
258

FIG. 49D

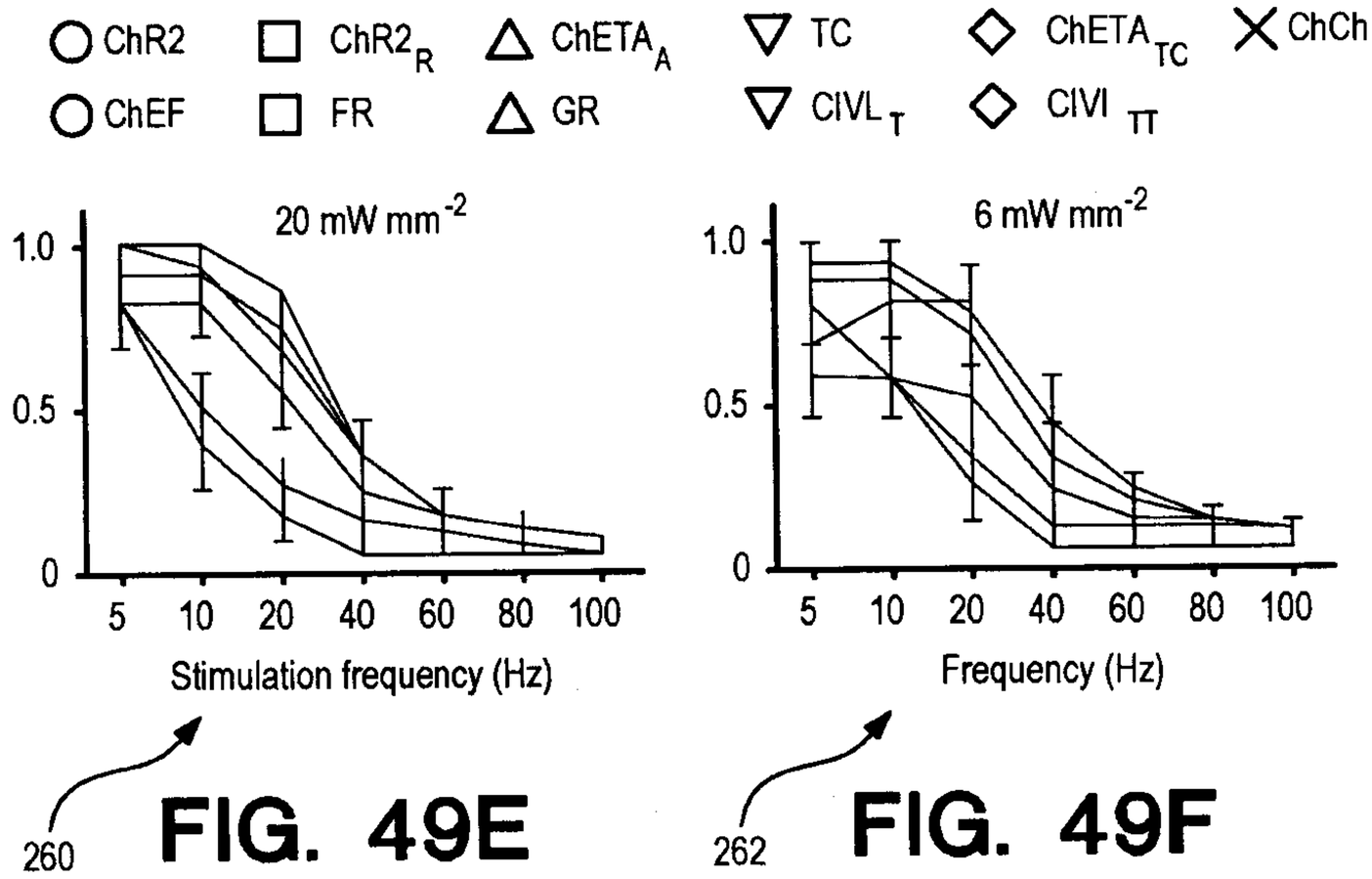


FIG. 49E

FIG. 49F

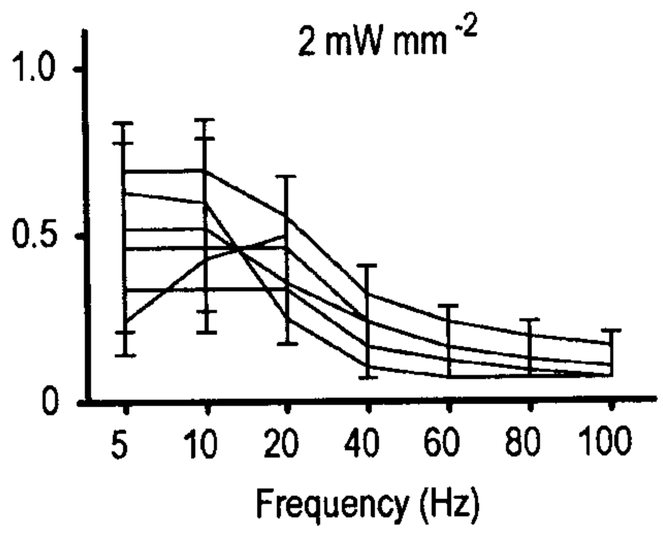


FIG. 49G

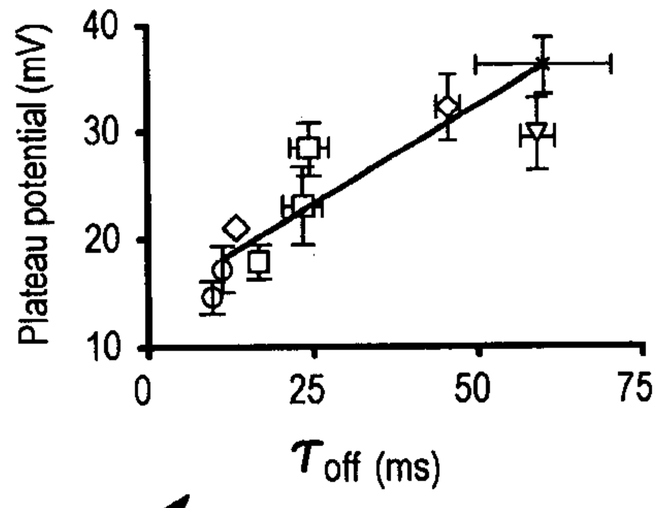


FIG. 49H

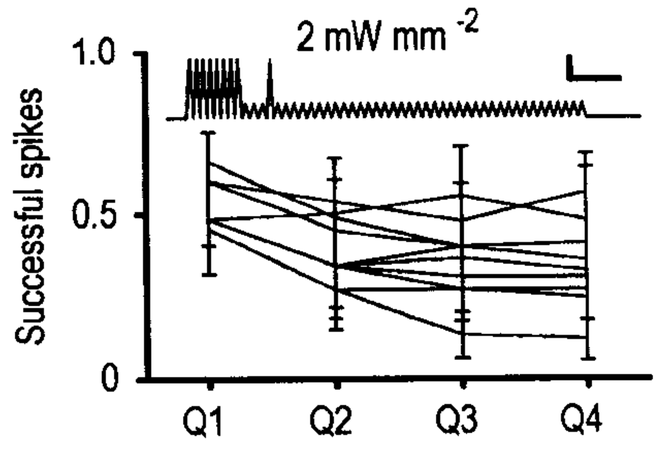


FIG. 49I

FIG. 49J

τ_{off}	Excite	Inhibit	Biochemical Modulation
Fast (~1-100 millisecond τoff)	by depolarization: ChR2 ChR2 (H134R) ChETAs: ChR2 (E123A) ChR2 (E123T) ChIEF ChRFR (FR, channelrhodopsin-fast receiver) ChRGR (GR, channelrhodopsin-green receiver) ChRWR (channelrhodopsin-wide receiver) VChR1 C1V1 C1V1 ChETA (E162T) C1V1 ChETA (E122T/E162T) ChR2 (T159C) ChR2 (L132C) (CatCH) ChR2 (E123T/T159C) ReaChR VCOMET DChR1	by hyperpolarization NpHR Arch ArchT eBR GtR3 (Guillardia theta Rhodopsin 3) Mac by depolarization block: ChR2 ChR2 (H134R) ChETAs: ChR2 (E123A) ChR2 (E123T) ChIEF ChRFR (FR, channelrhodopsin-fast receiver) ChRGR (GR, channelrhodopsin-green receiver) ChRWR (channelrhodopsin-wide receiver) VChR1 C1V1 C1V1 ChETA (E162T) C1V1 ChETA (E122T/E162T) ChR2 (T159C) ChR2 (L132C)(CatCH) ChR2 (E123T/T159C) ReaChR VCOMET DChR1 Champ	
Slow (~1-100 second τoff)	by depolarization: ChR2-step function opsins ChR2 (C128A) ChR2 (C128S) ChR2 (D156A) ChR2 (C128T) VCHR1-step function	by depolarization block: ChR2-step function opsins ChR2 (C128A) ChR2 (C128S) ChR2 (D156A) ChR2 (C128T) VChR1-step function opsins VChR1 (C123S)	Optoβ 2AR Optoα 1AR Rh-CT(5-HT1A) bPAC BlaC

	opsins VChR1 (C123S)	By hyperpolarization: SwiChR (iC1C2)	
Very Slow (~minutes τ off)	by depolarization: ChR2 (D156A/C128S) (SSFO) VChR1 (C123S/D151A) (VSSFO)	by depolarization block: ChR2 (D156A/C128S)(SSFO) VChR1 (C123S/D151A)(VSSFO)	

FIG. 49J CONTINUED

1024

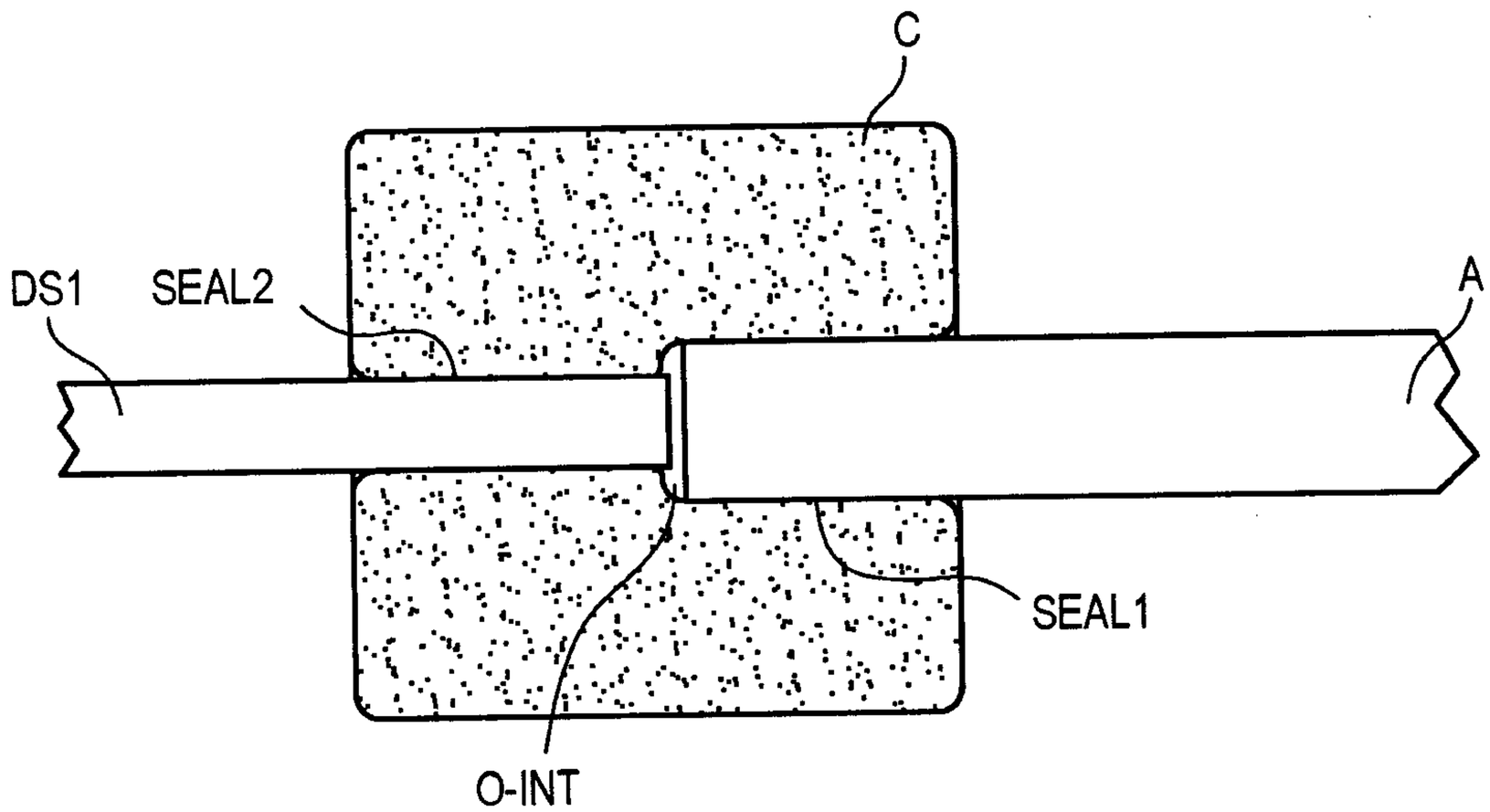

C
DS1
SEAL2
A
SEAL1
O-INT

FIG. 50

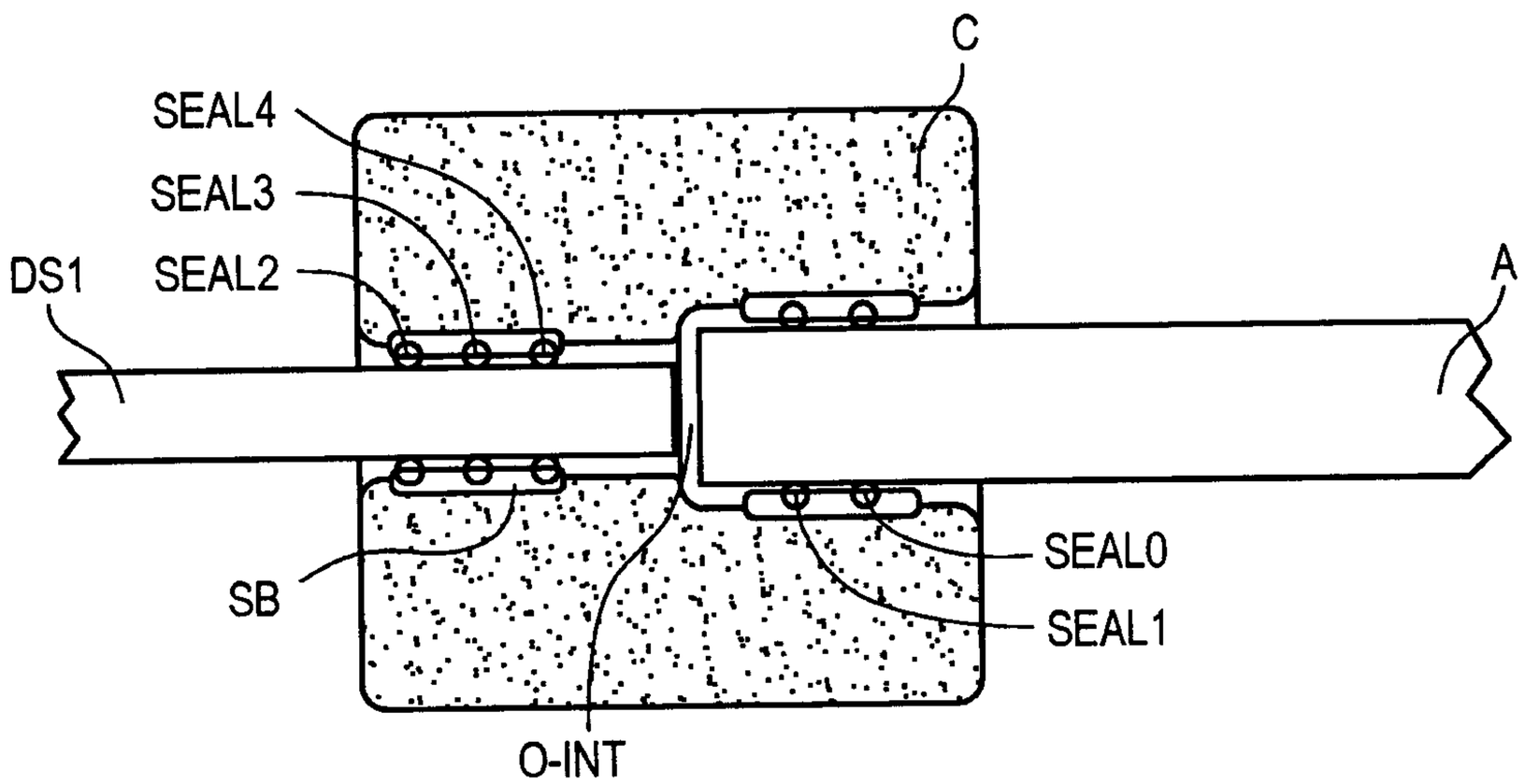

C
SEAL4
SEAL3
DS1
SEAL2
A
SEAL0
SB
SEAL1
O-INT

FIG. 51

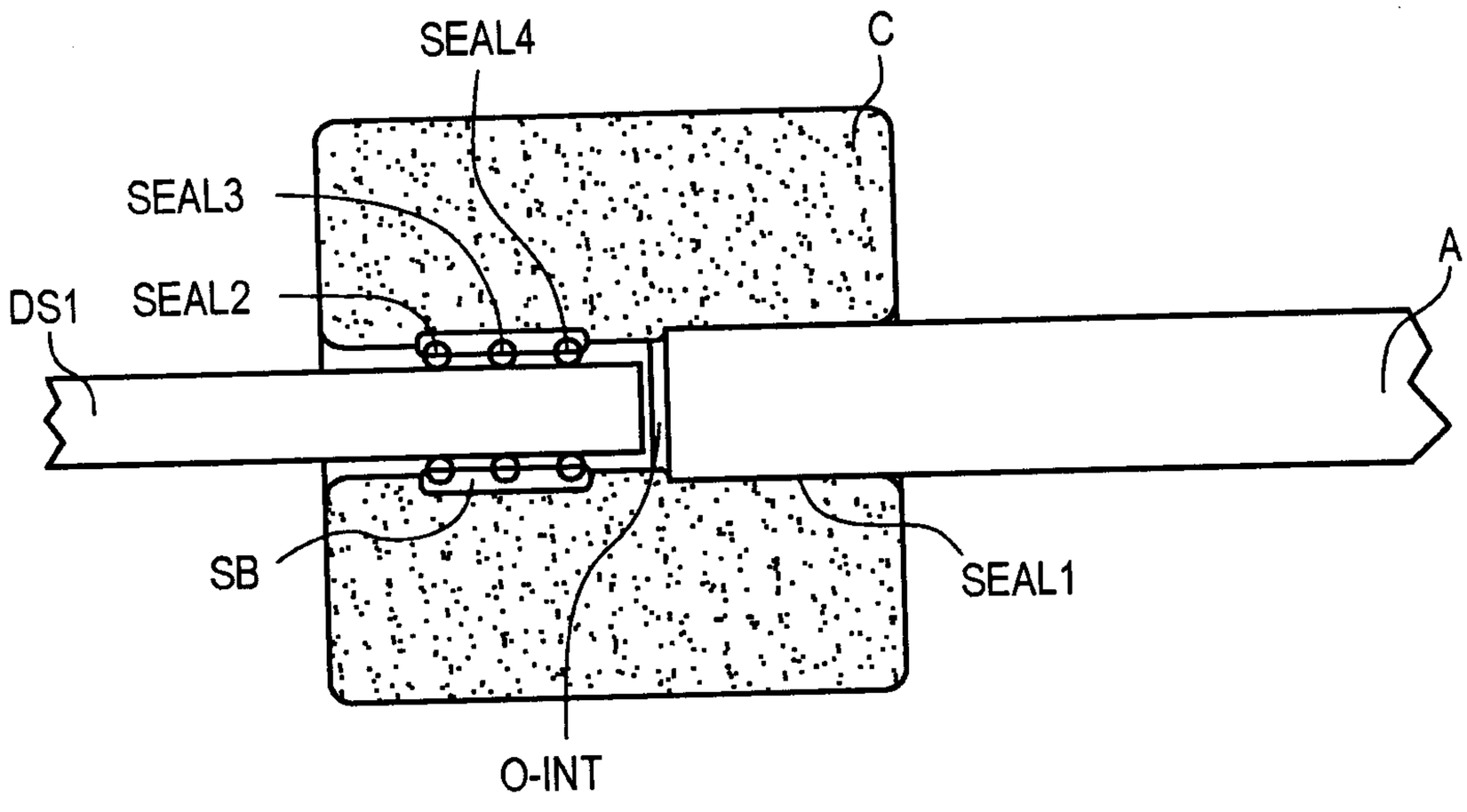

SEAL4
C
SEAL3
A
DS1
SEAL2
SB
SEAL1
O-INT

FIG. 52

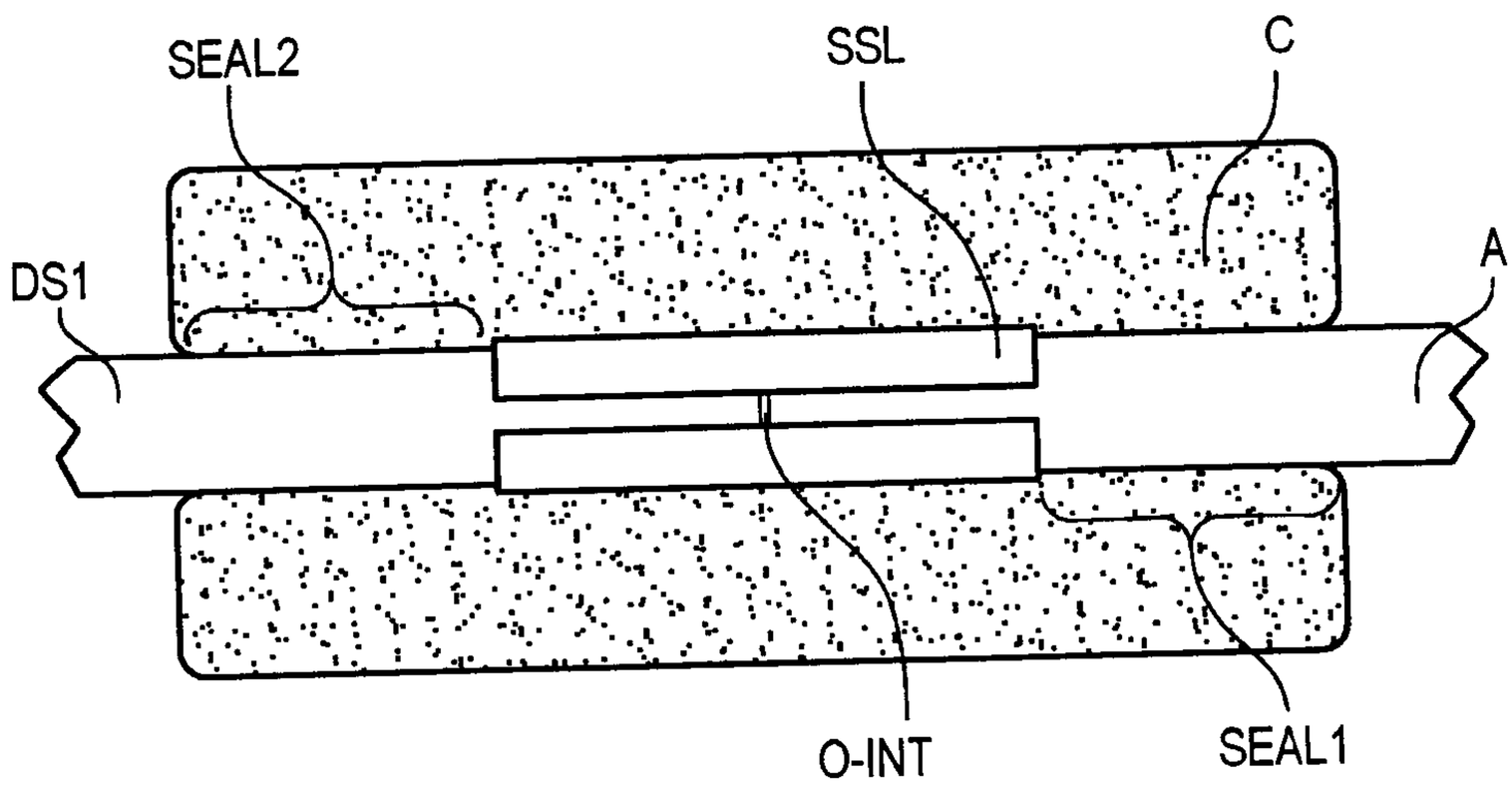

SEAL2
SSL
C
DS1
A
O-INT
SEAL1

FIG. 53

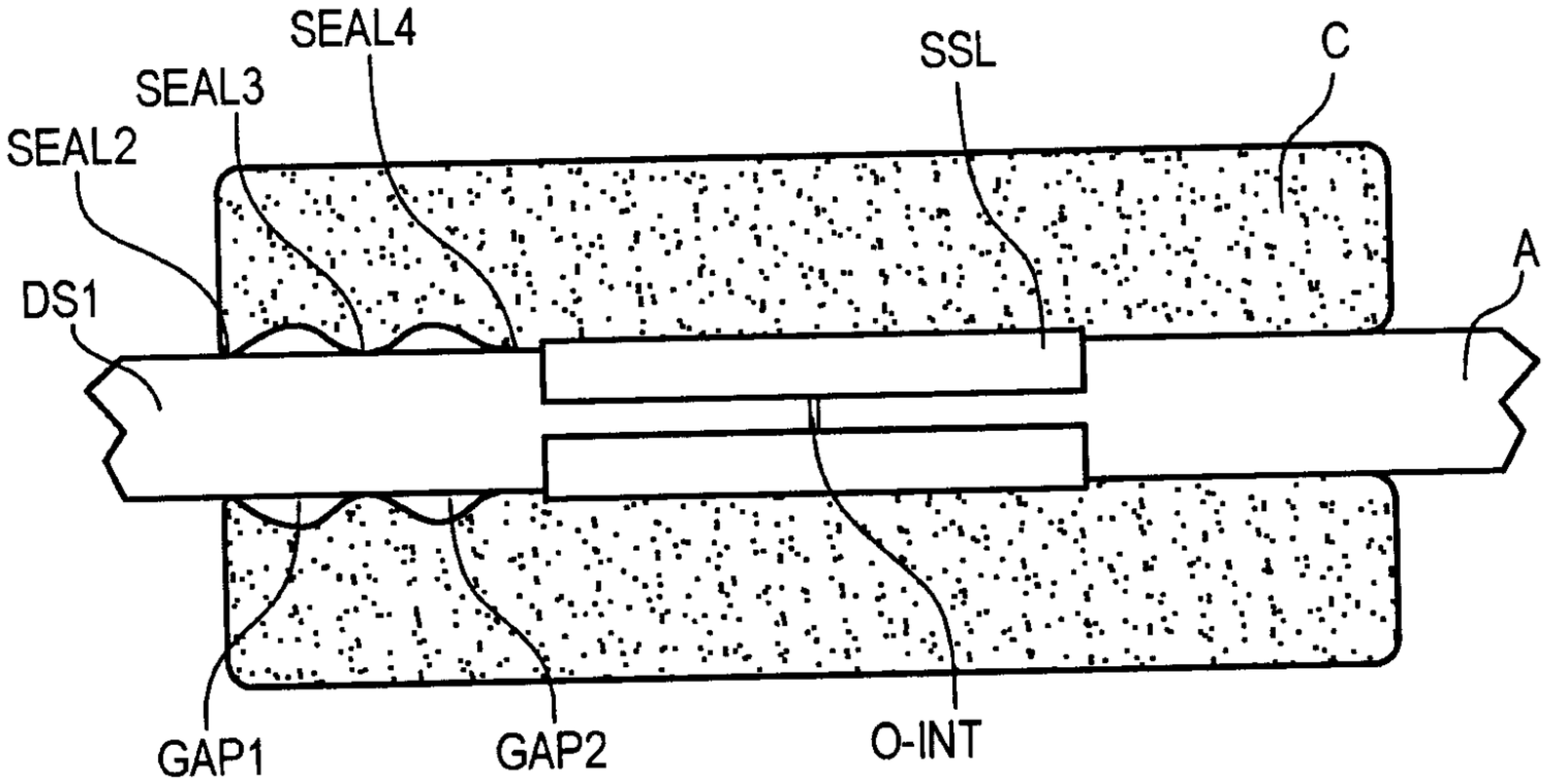

SEAL4
SSL
C
SEAL3
SEAL2
A
DS1
GAP1
GAP2
O-INT

FIG. 54

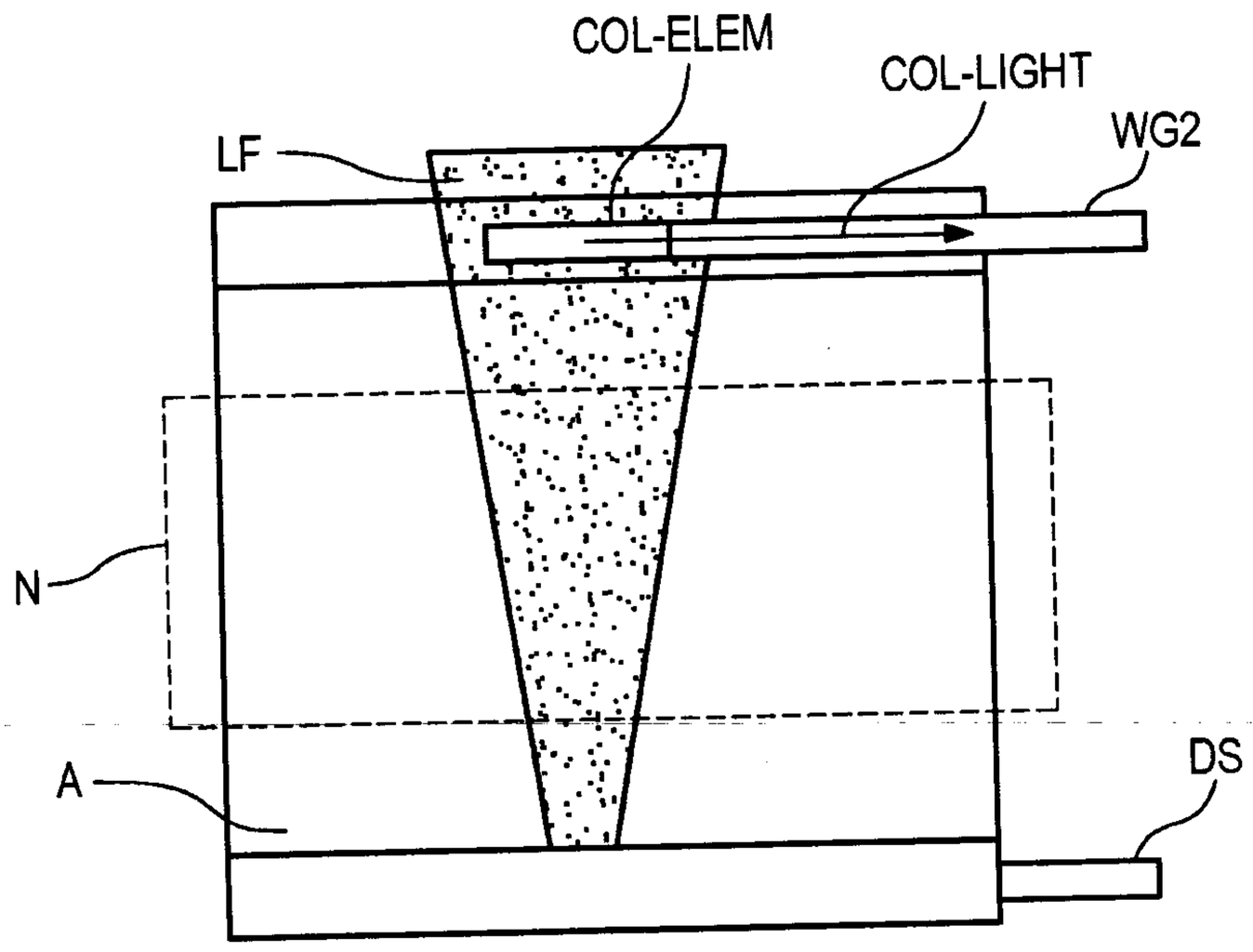

COL-ELEM
COL-LIGHT
WG2
LF
N
A
DS

FIG. 55

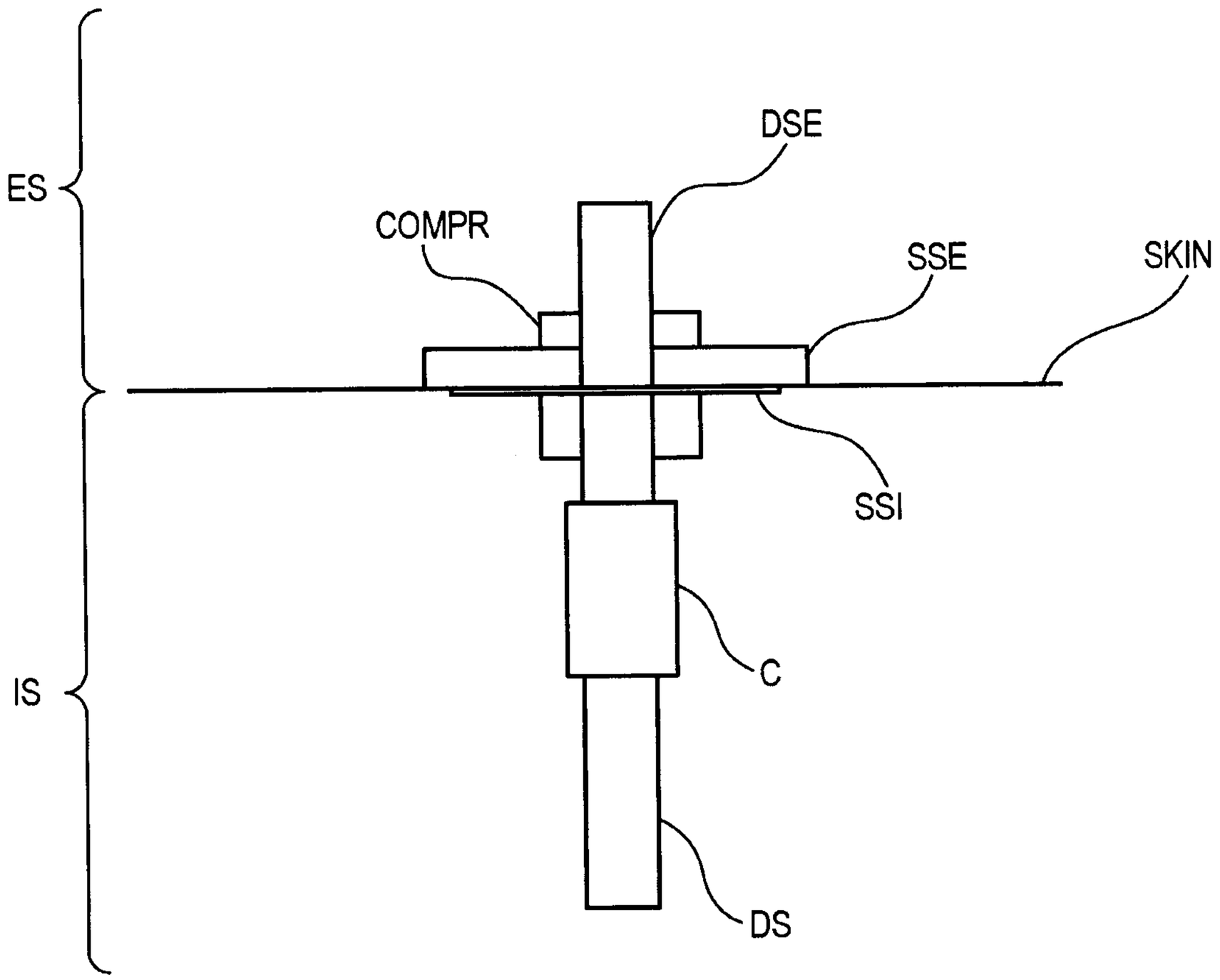


FIG. 56

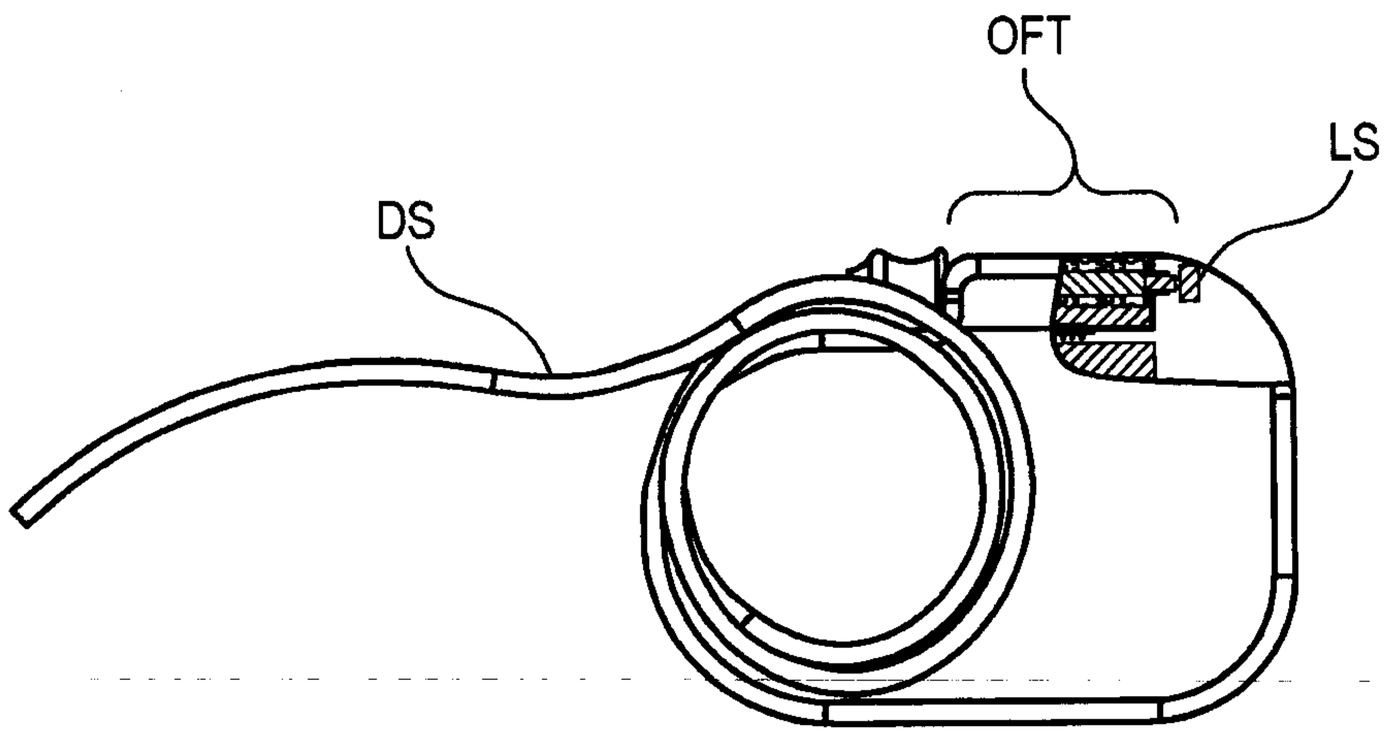


FIG. 57A

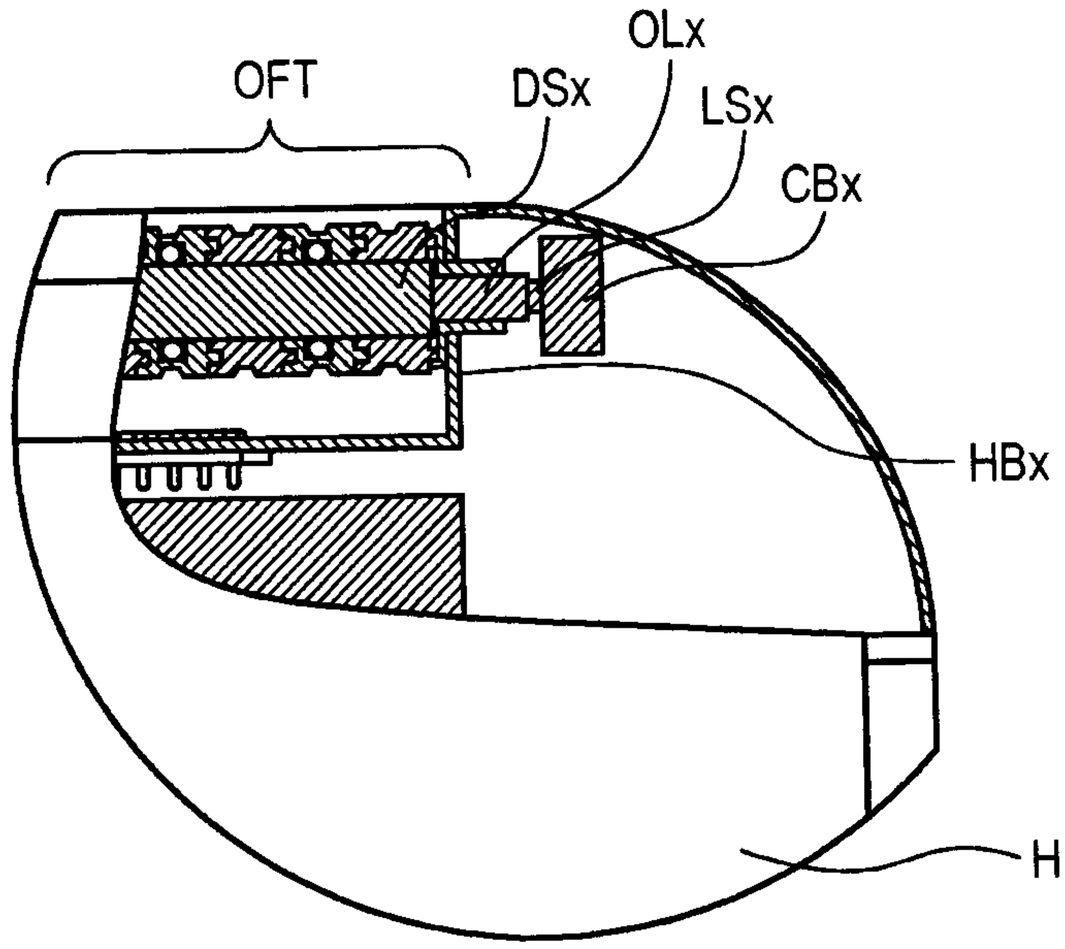


FIG. 57B

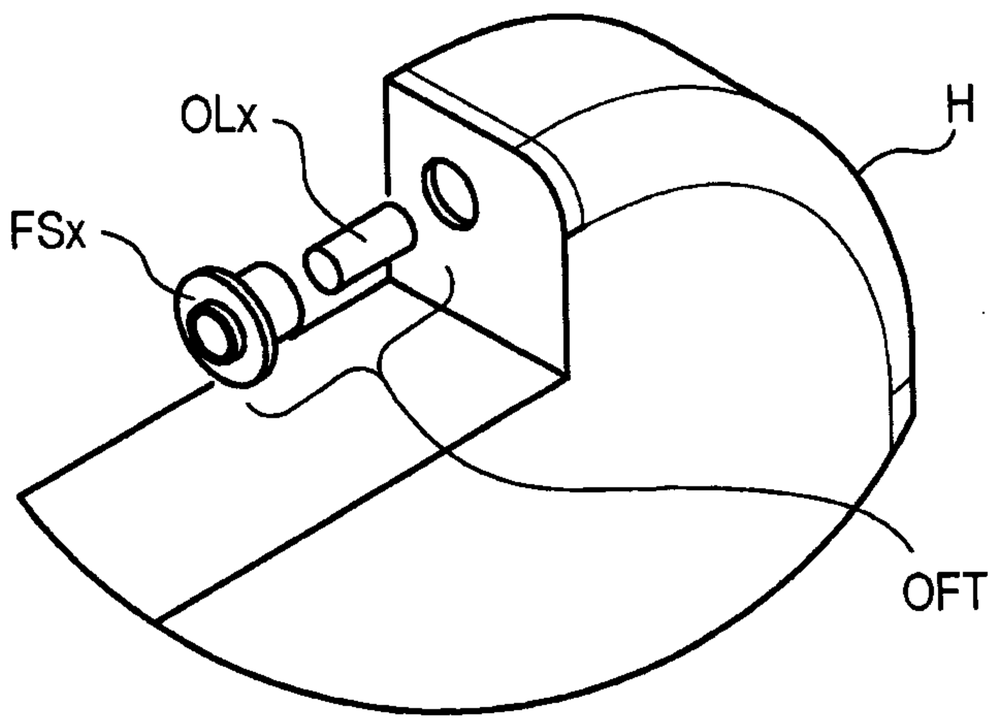


FIG. 58

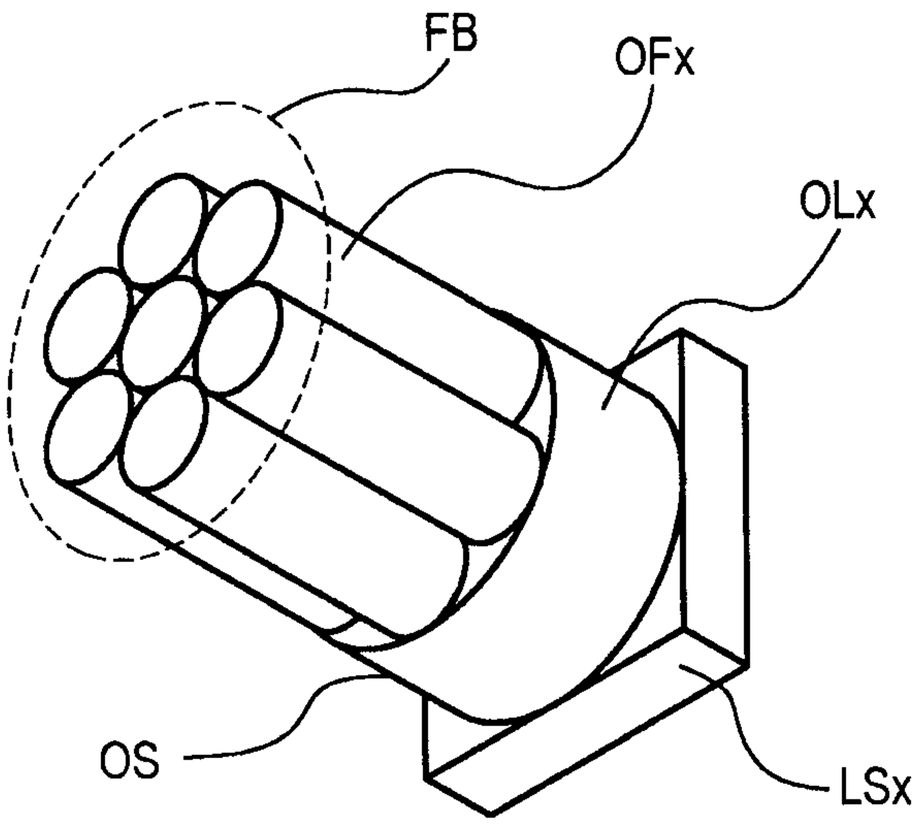


FIG. 59

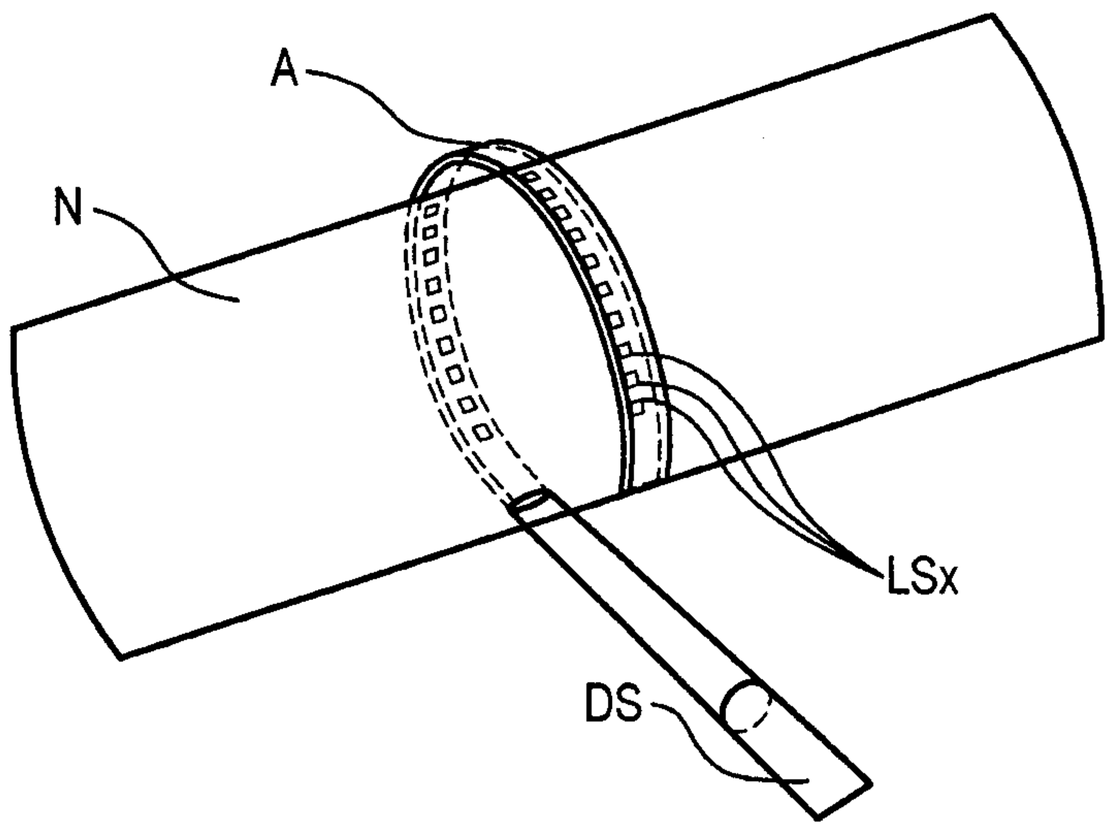


FIG. 60

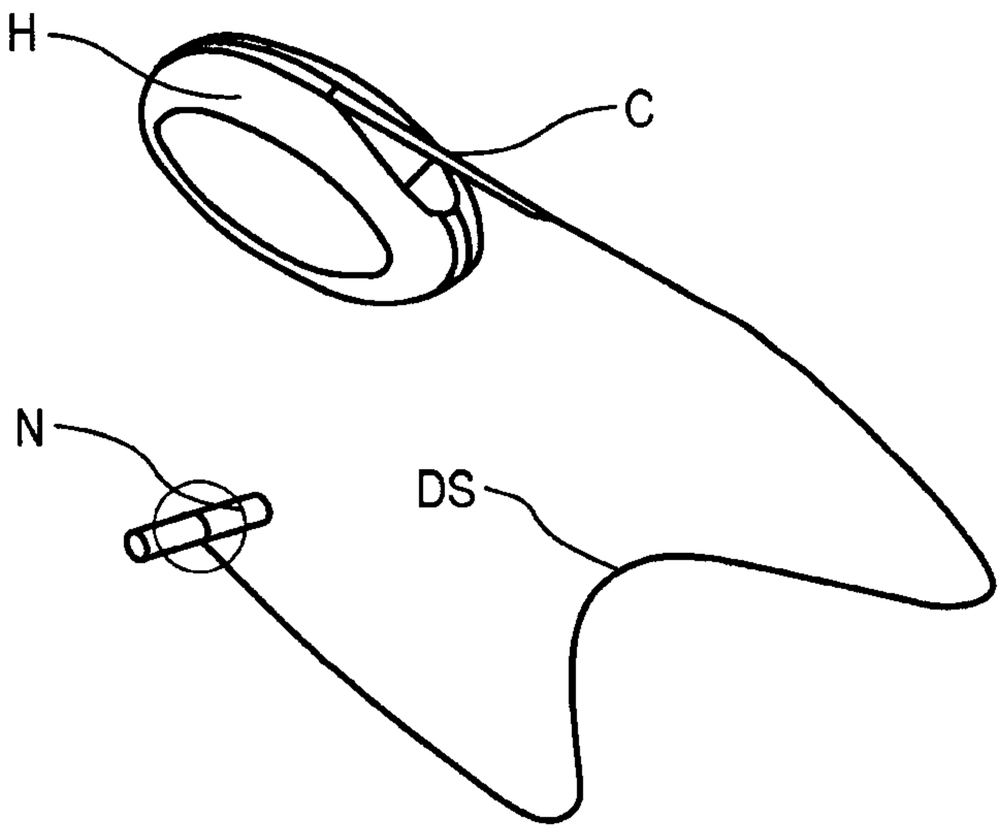


FIG. 61

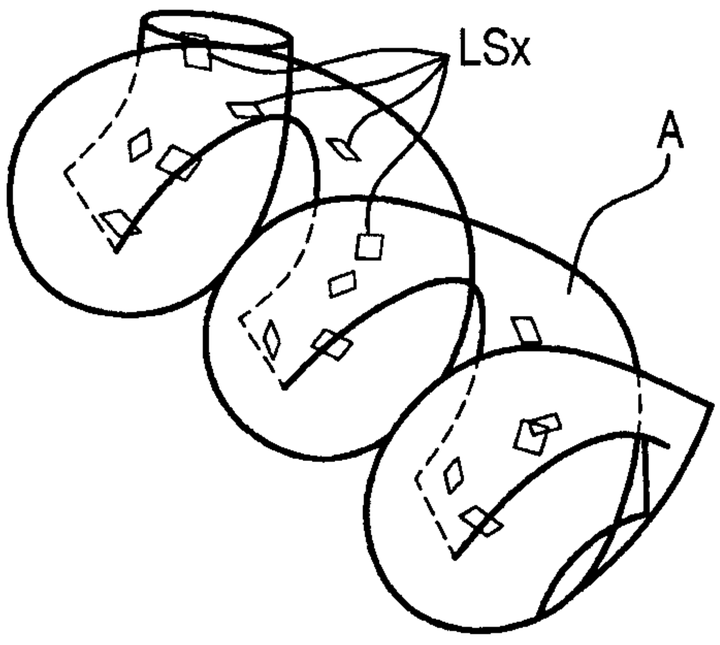


FIG. 62

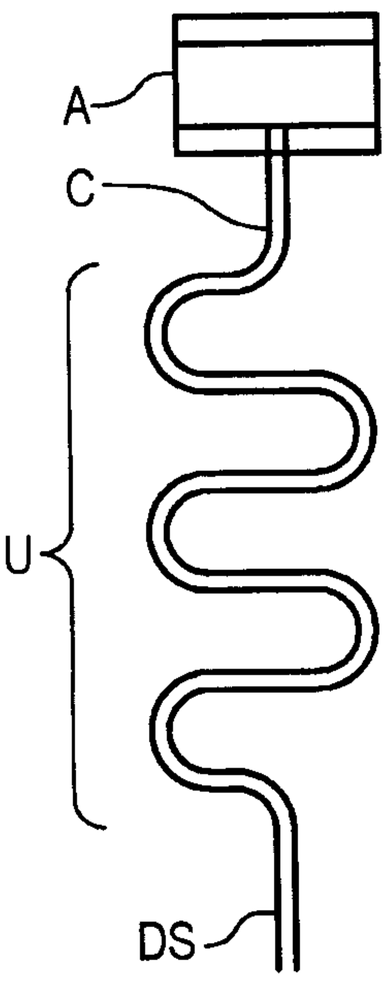


FIG. 63A

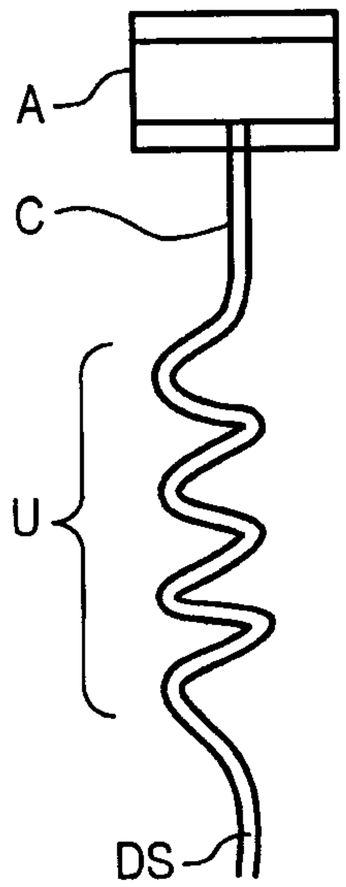


FIG. 63B

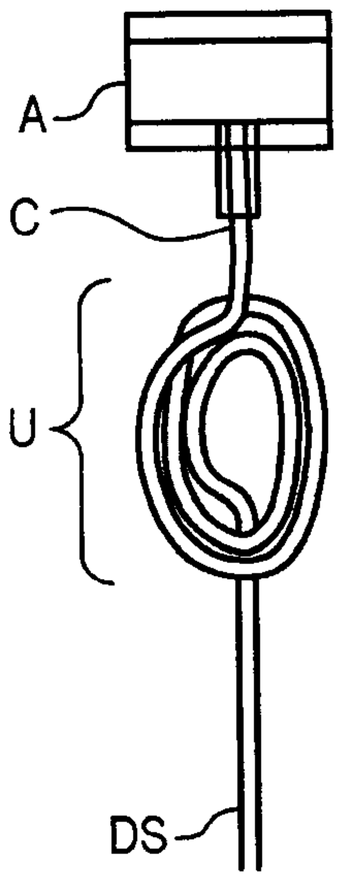


FIG. 63C

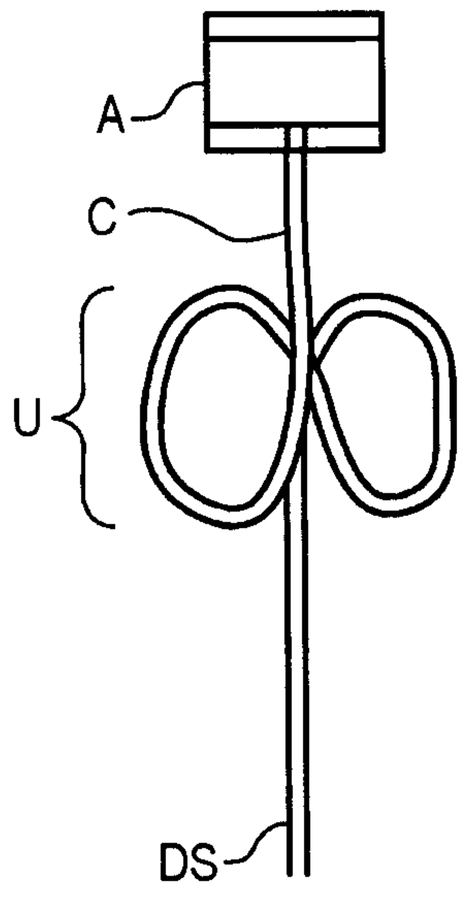


FIG. 63D

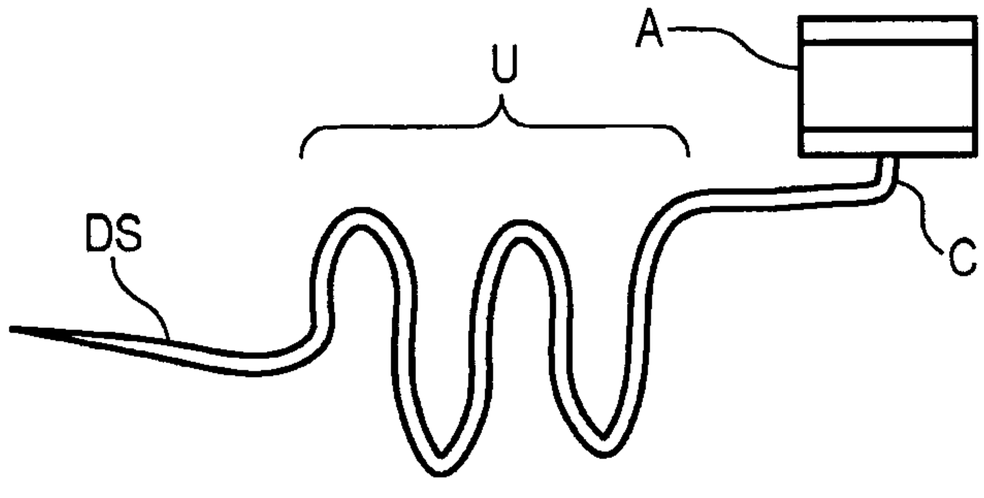


FIG. 64

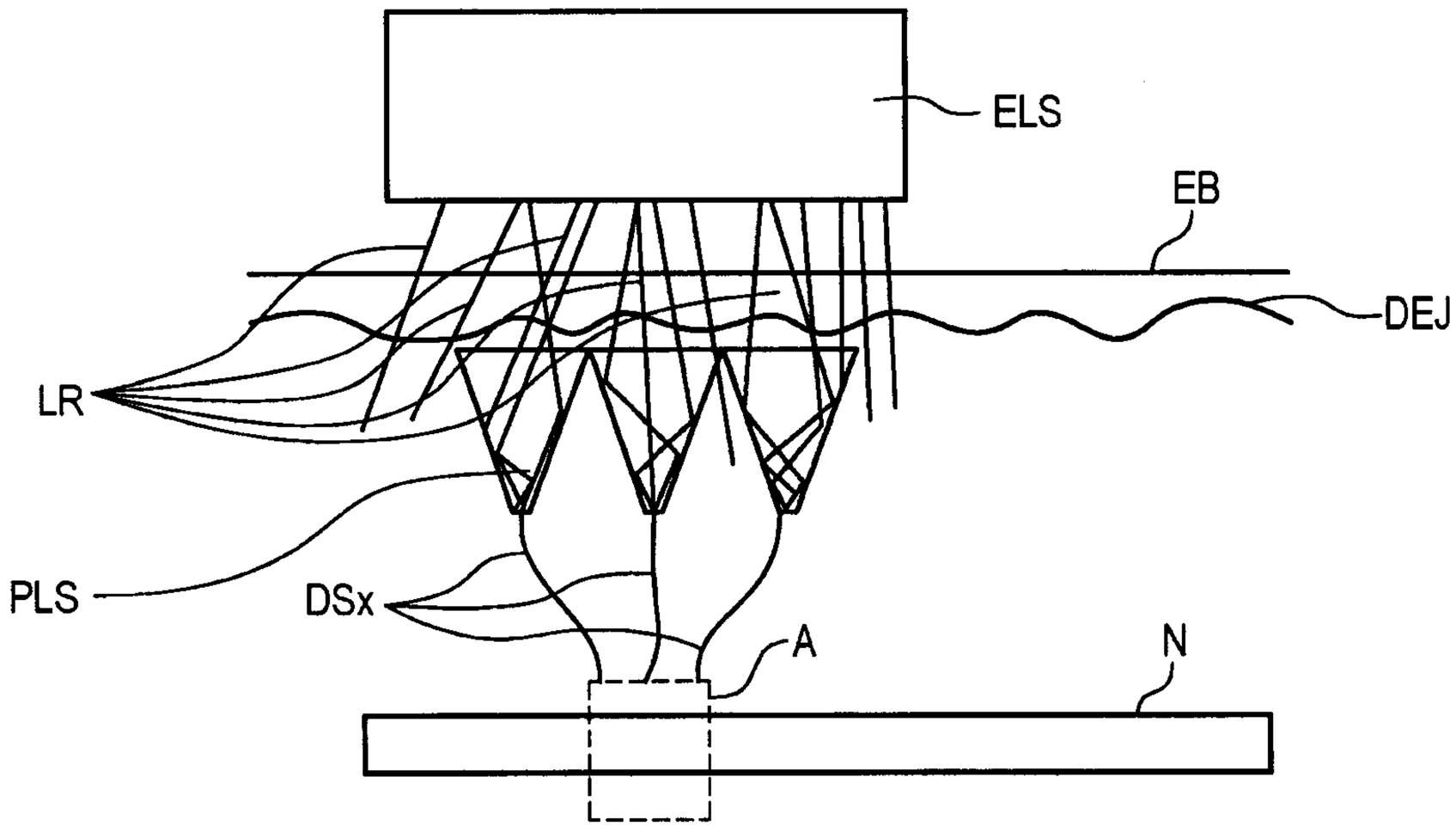


FIG. 65

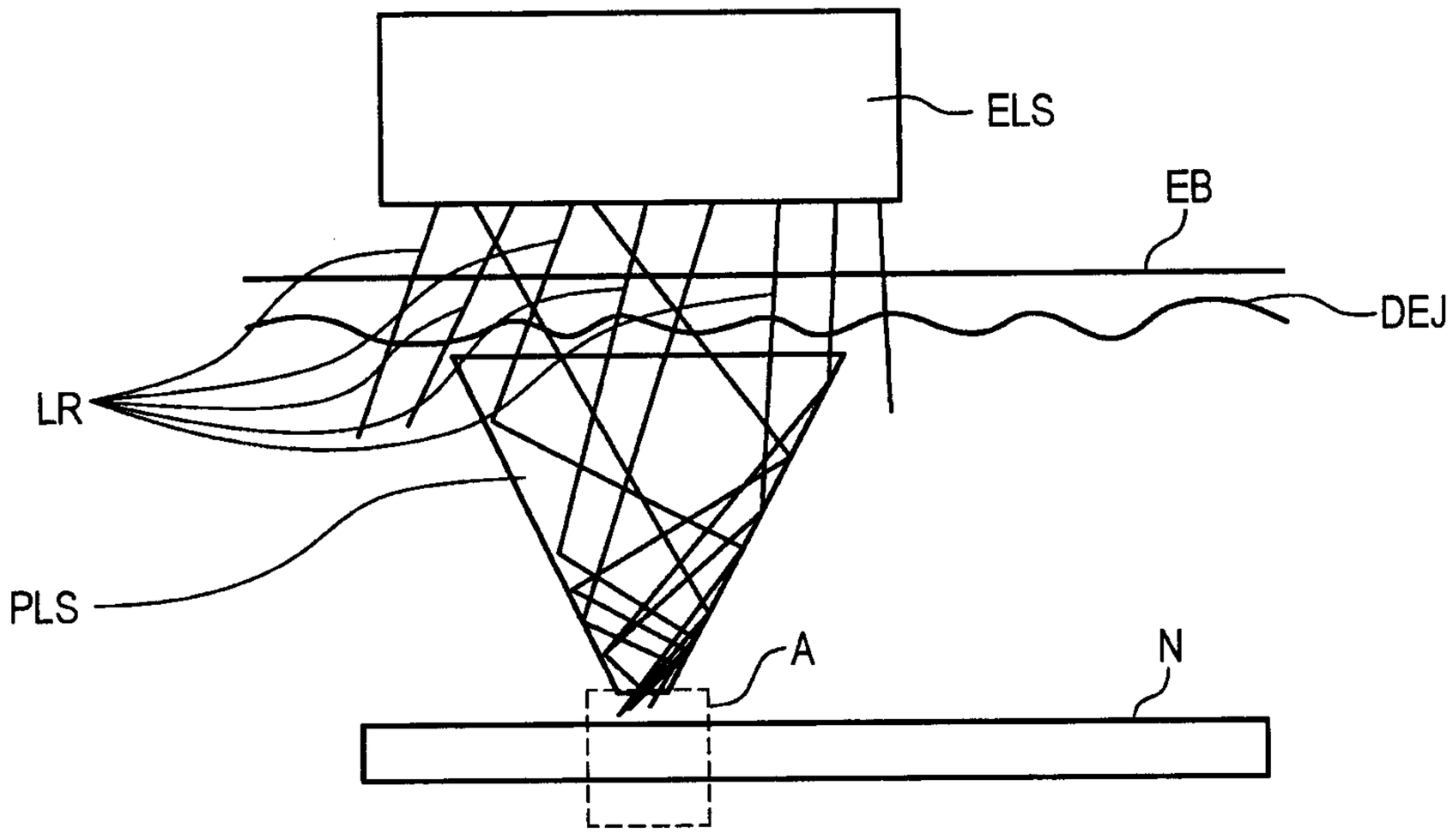


FIG. 66

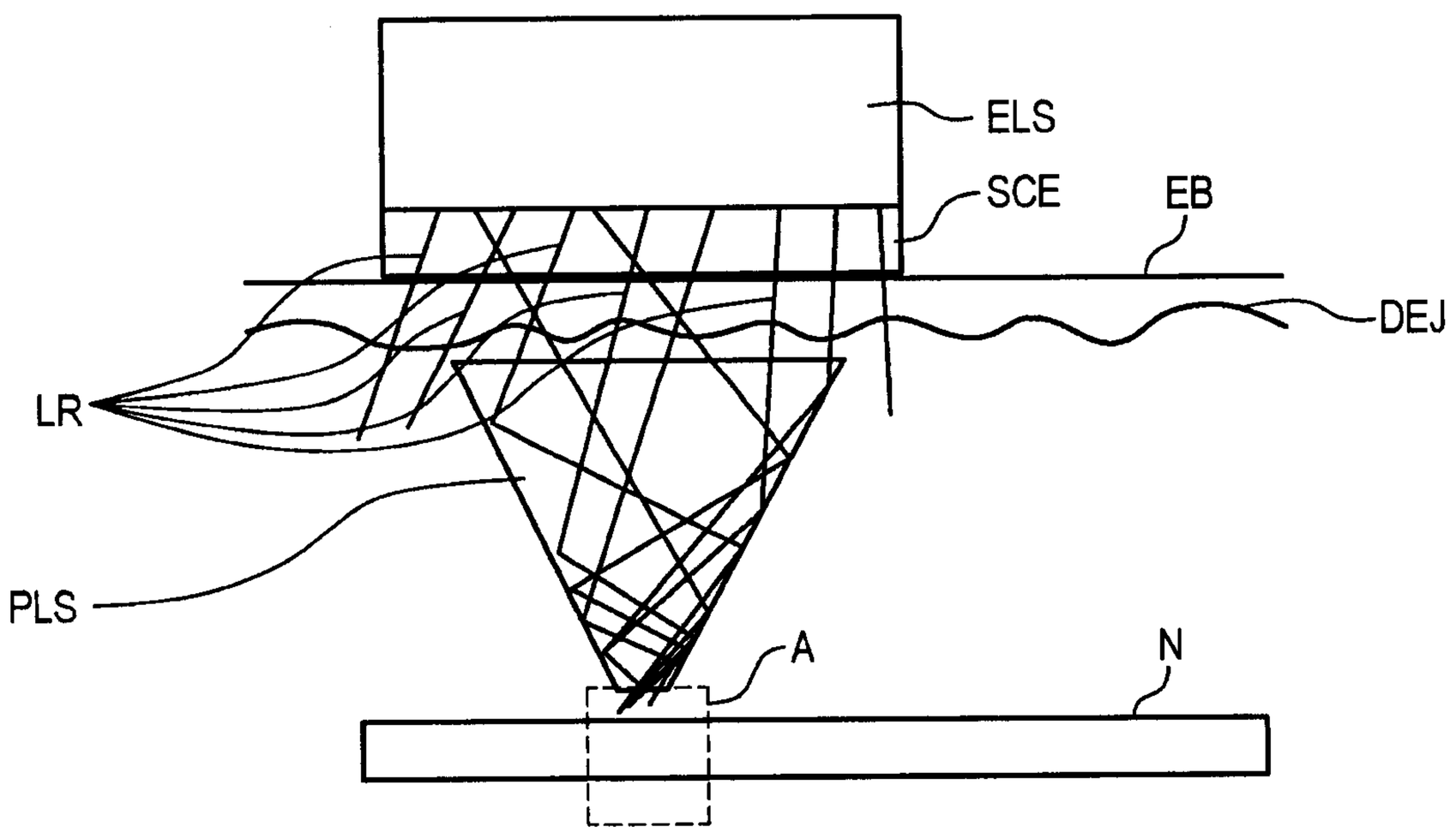


FIG. 67

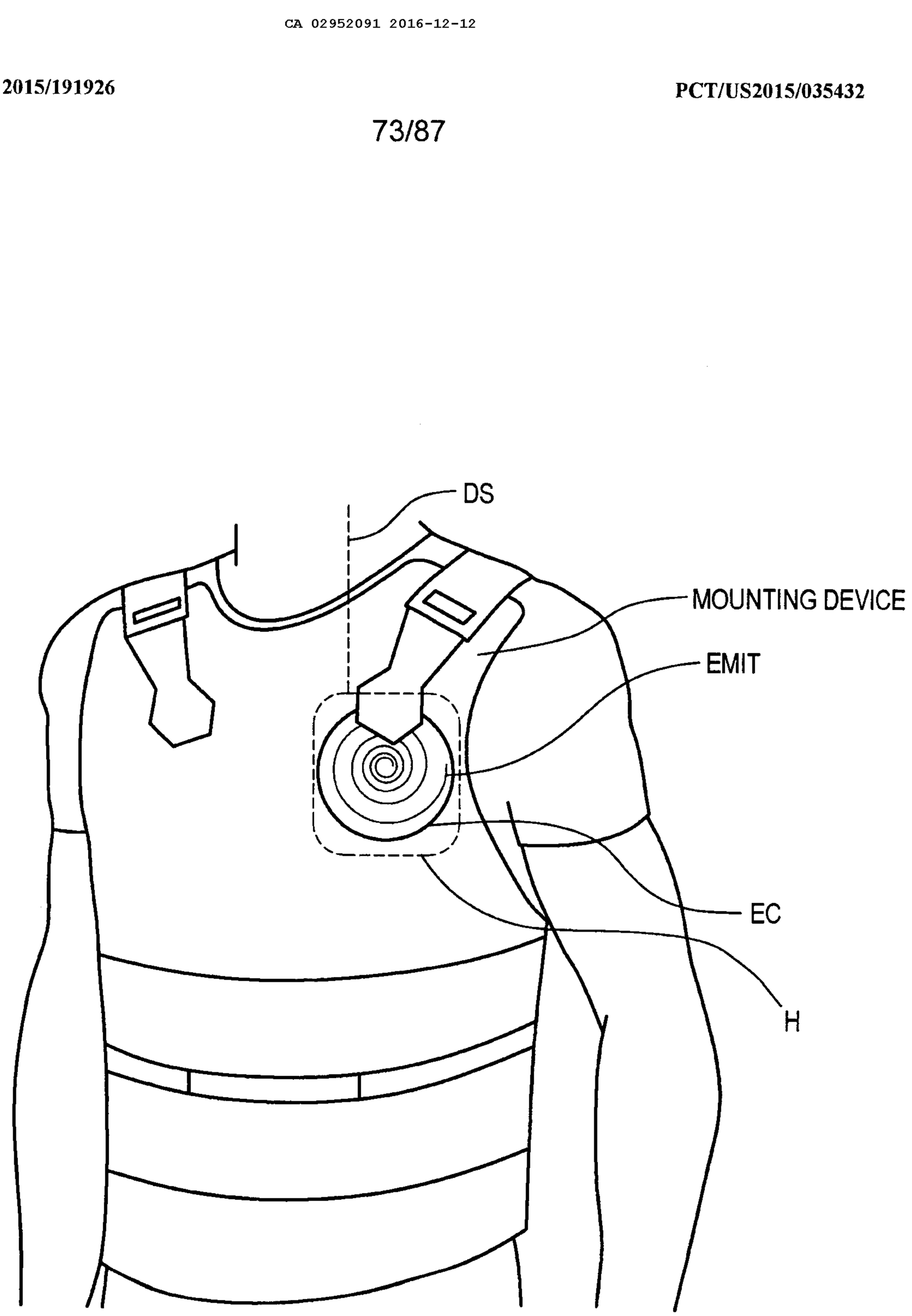


FIG. 68

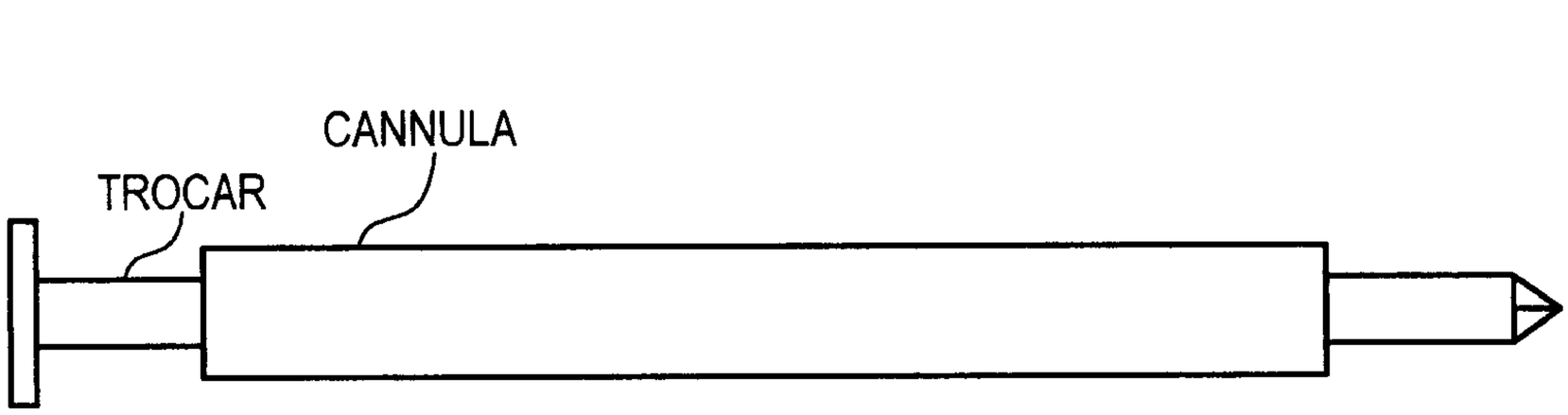


FIG. 69A

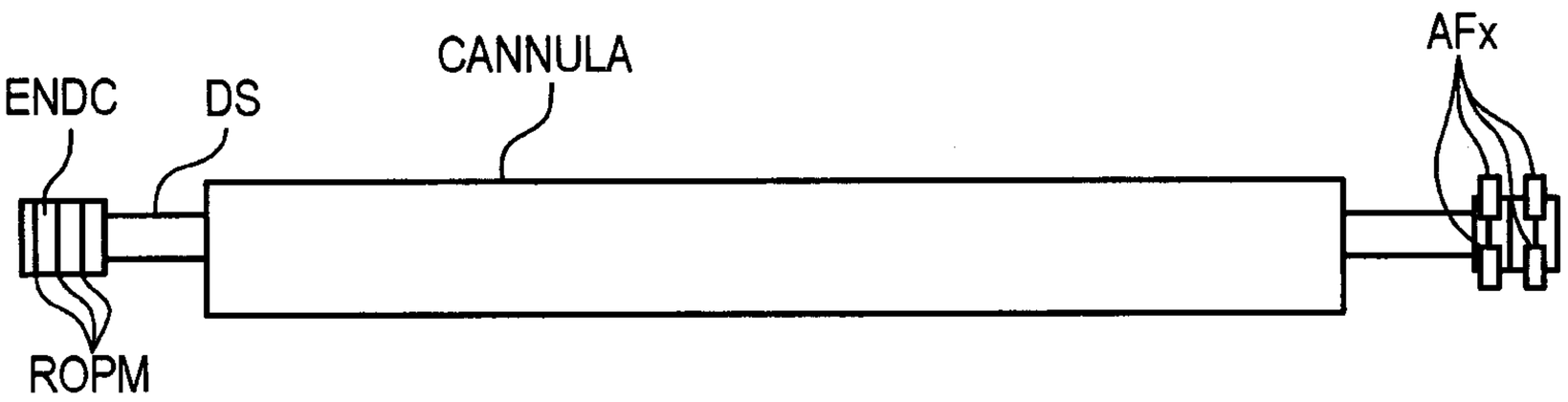


FIG. 69B

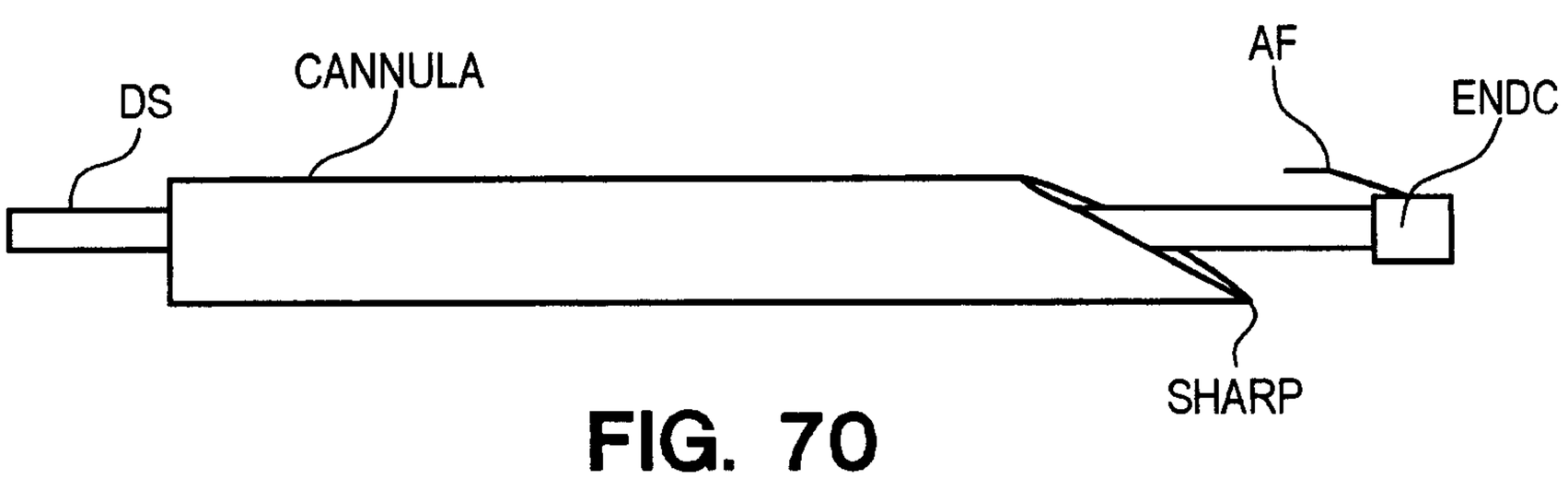


FIG. 70

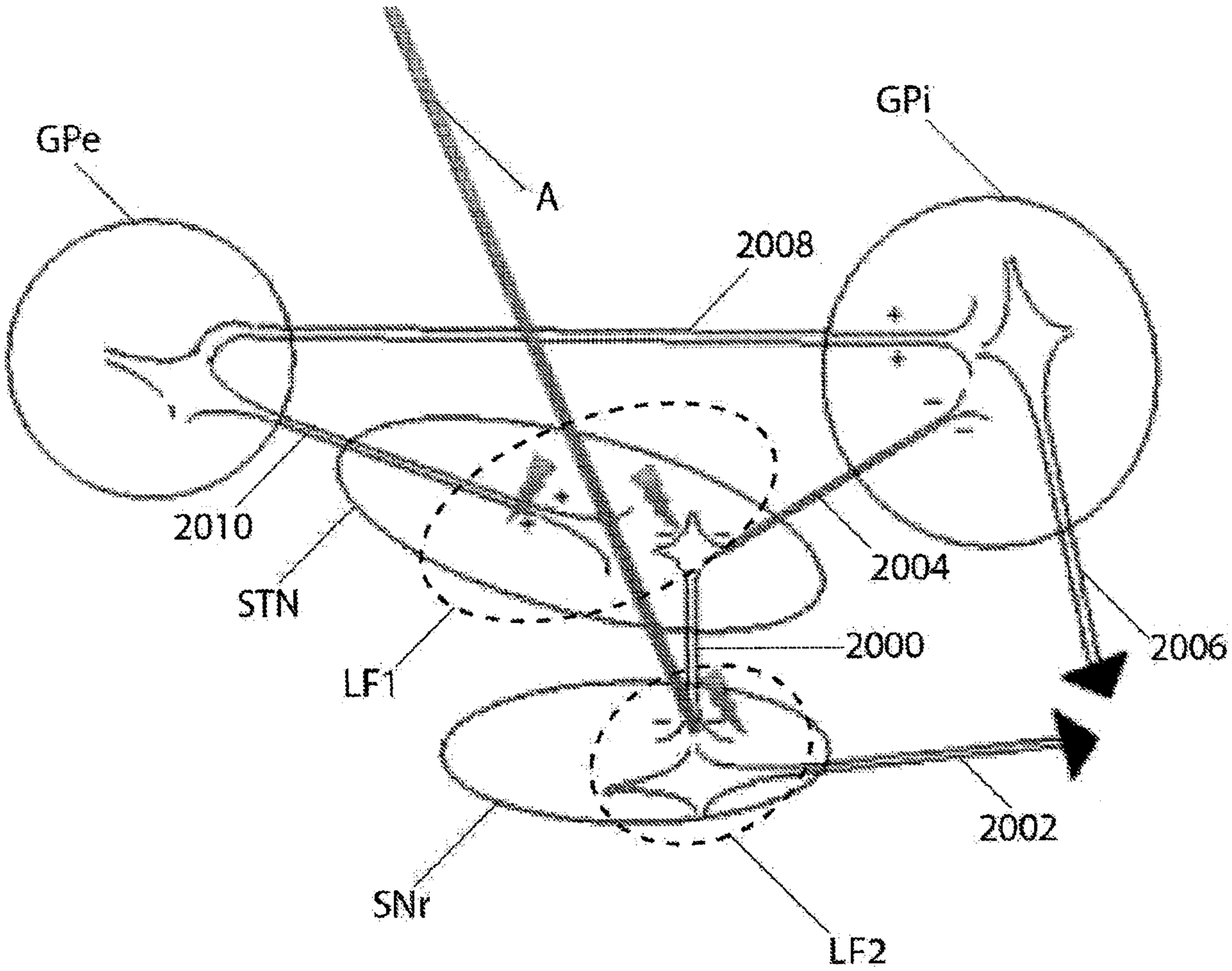


Figure 71

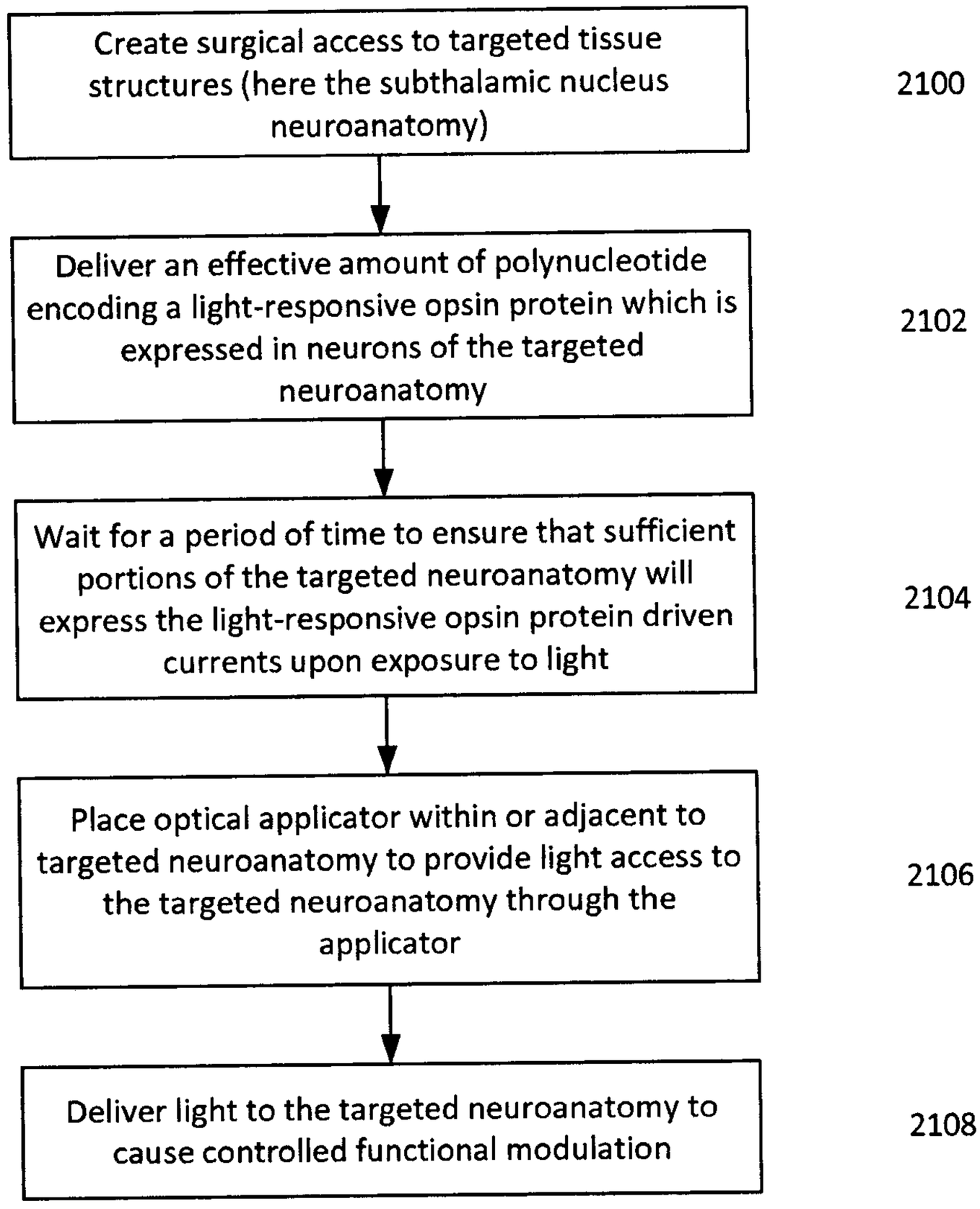

Create surgical access to targeted tissue structures (here the subthalamic nucleus neuroanatomy)
2100
Deliver an effective amount of polynucleotide encoding a light-responsive opsin protein which is expressed in neurons of the targeted neuroanatomy
2102
Wait for a period of time to ensure that sufficient portions of the targeted neuroanatomy will express the light-responsive opsin protein driven currents upon exposure to light
2104
Place optical applicator within or adjacent to targeted neuroanatomy to provide light access to the targeted neuroanatomy through the applicator
2106
Deliver light to the targeted neuroanatomy to cause controlled functional modulation
2108

Figure 72A

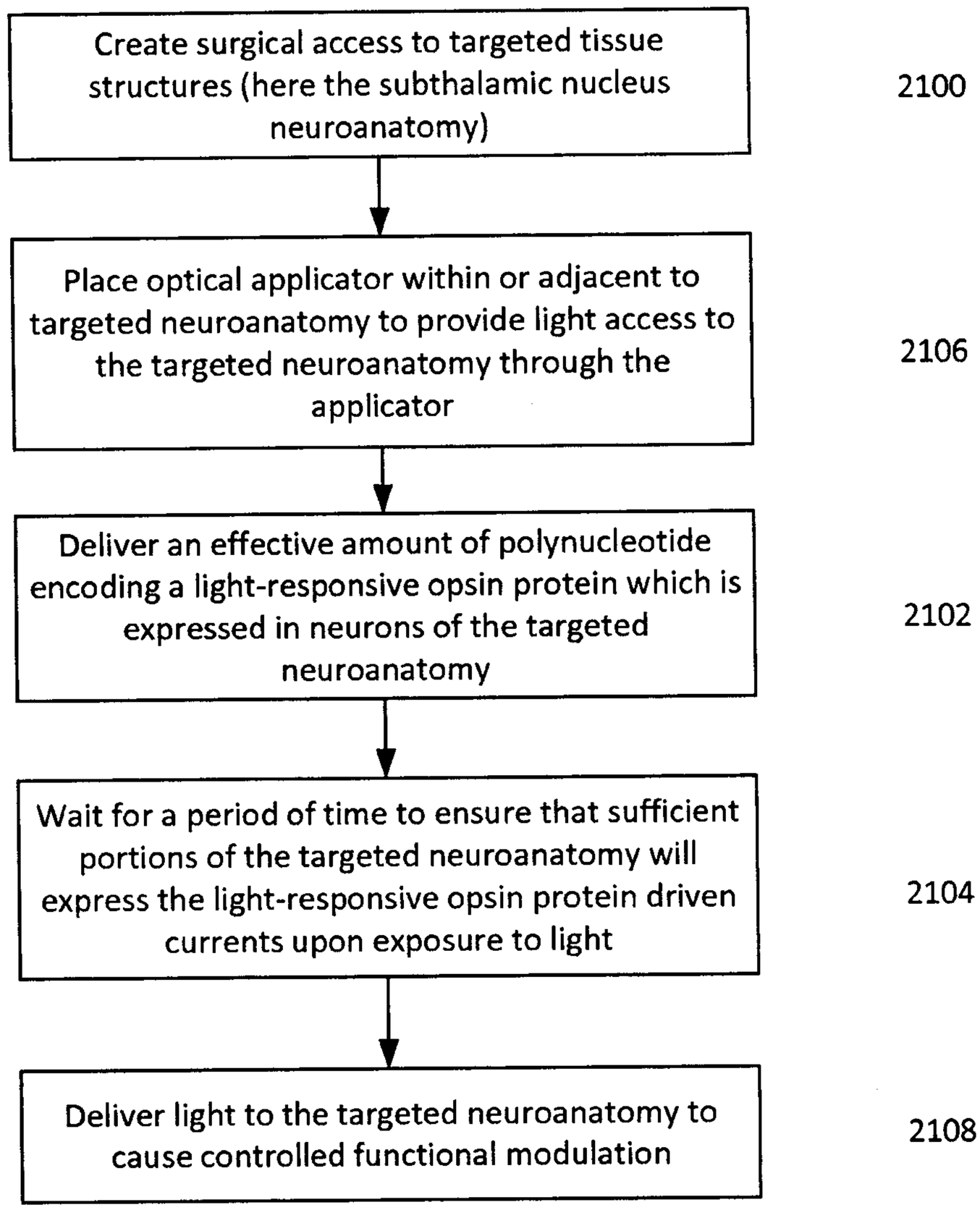

Create surgical access to targeted tissue structures (here the subthalamic nucleus neuroanatomy)
2100
Place optical applicator within or adjacent to targeted neuroanatomy to provide light access to the targeted neuroanatomy through the applicator
2106
Deliver an effective amount of polynucleotide encoding a light-responsive opsin protein which is expressed in neurons of the targeted neuroanatomy
2102
Wait for a period of time to ensure that sufficient portions of the targeted neuroanatomy will express the light-responsive opsin protein driven currents upon exposure to light
2104
Deliver light to the targeted neuroanatomy to cause controlled functional modulation
2108

Figure 72B

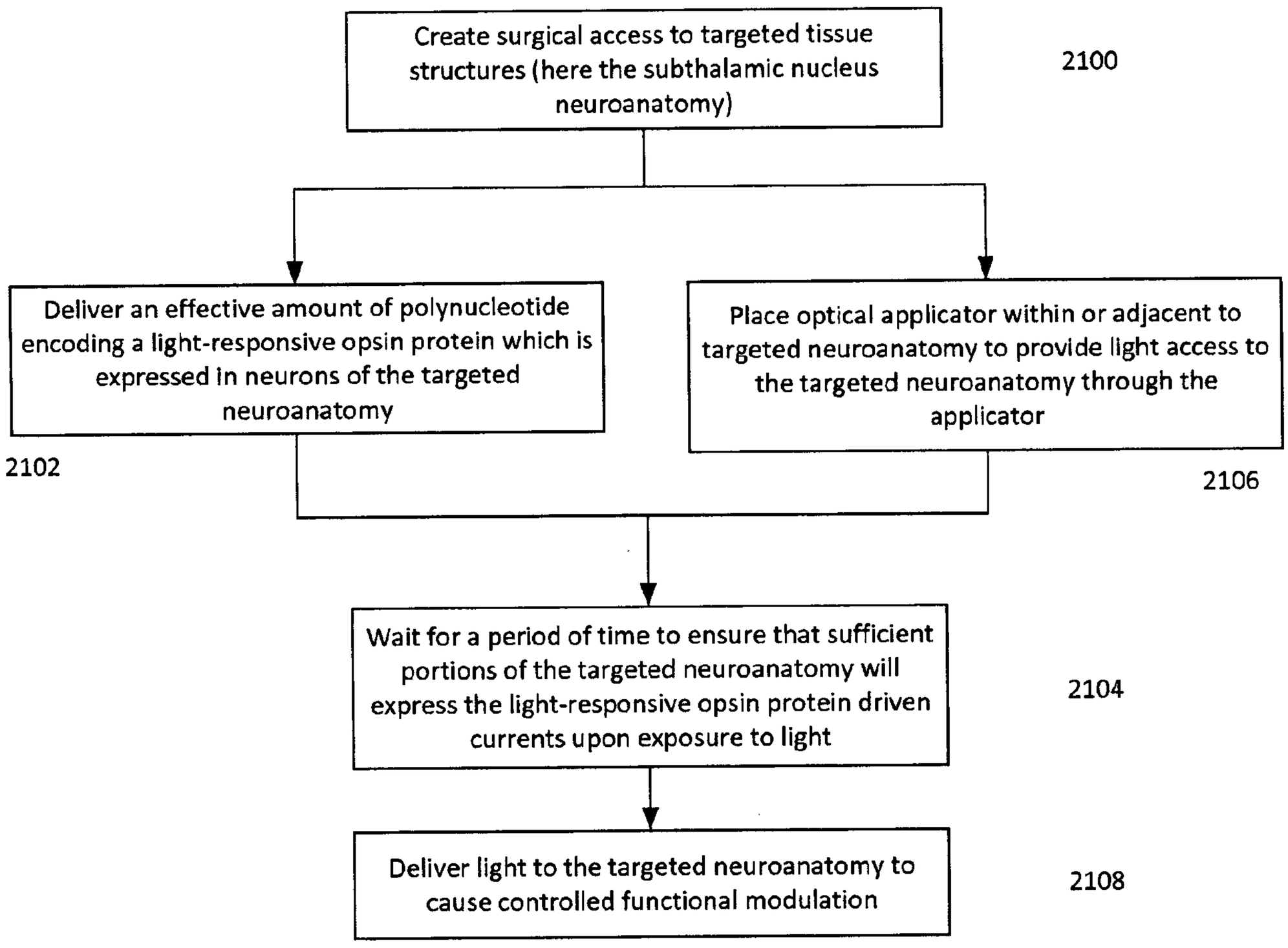

Create surgical access to targeted tissue structures (here the subthalamic nucleus neuroanatomy)
2100
Deliver an effective amount of polynucleotide encoding a light-responsive opsin protein which is expressed in neurons of the targeted neuroanatomy
2102
Place optical applicator within or adjacent to targeted neuroanatomy to provide light access to the targeted neuroanatomy through the applicator
2106
Wait for a period of time to ensure that sufficient portions of the targeted neuroanatomy will express the light-responsive opsin protein driven currents upon exposure to light
2104
Deliver light to the targeted neuroanatomy to cause controlled functional modulation
2108

Figure 72C

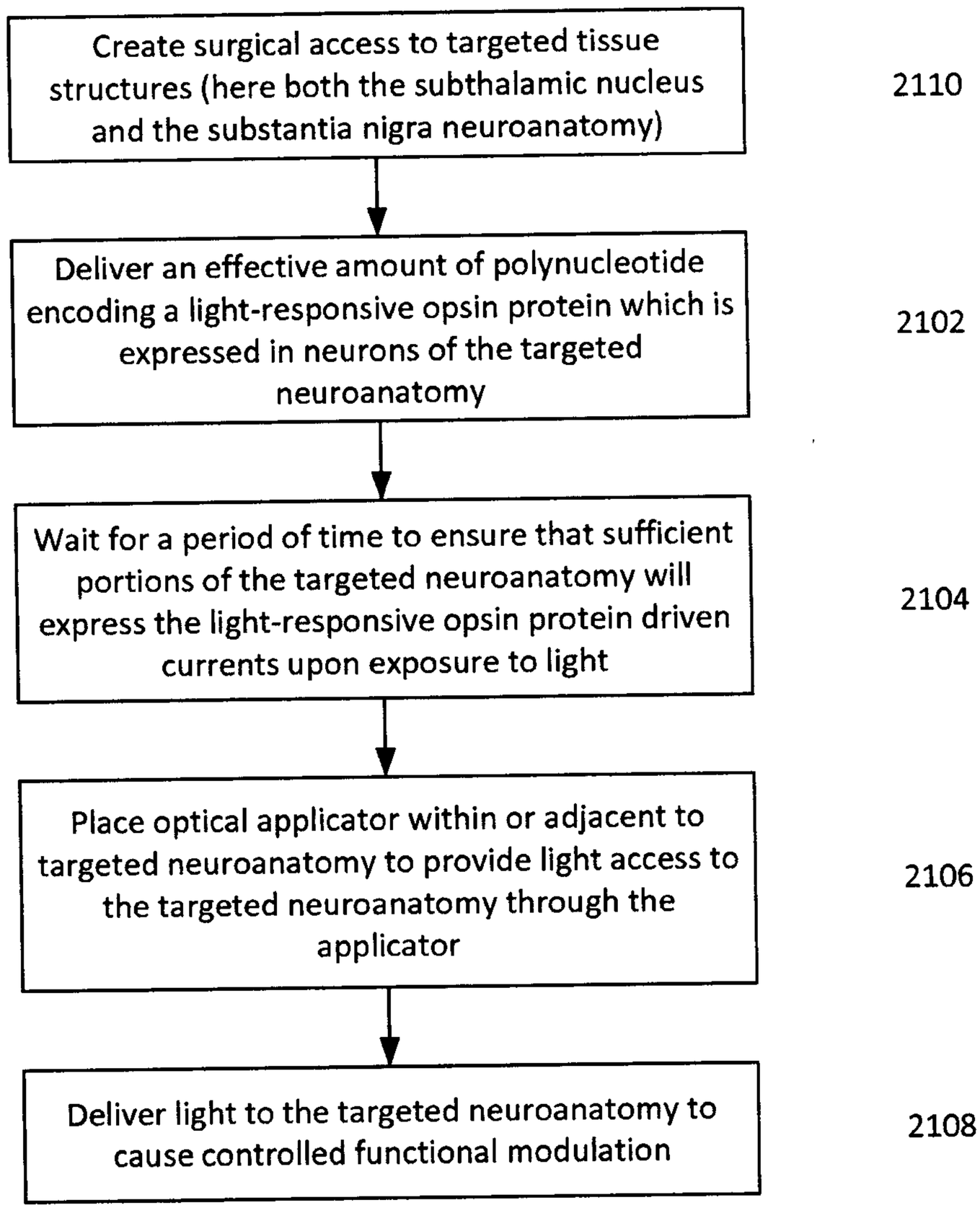

Create surgical access to targeted tissue structures (here both the subthalamic nucleus and the substantia nigra neuroanatomy)
2110
Deliver an effective amount of polynucleotide encoding a light-responsive opsin protein which is expressed in neurons of the targeted neuroanatomy
2102
Wait for a period of time to ensure that sufficient portions of the targeted neuroanatomy will express the light-responsive opsin protein driven currents upon exposure to light
2104
Place optical applicator within or adjacent to targeted neuroanatomy to provide light access to the targeted neuroanatomy through the applicator
2106
Deliver light to the targeted neuroanatomy to cause controlled functional modulation
2108

Figure 73

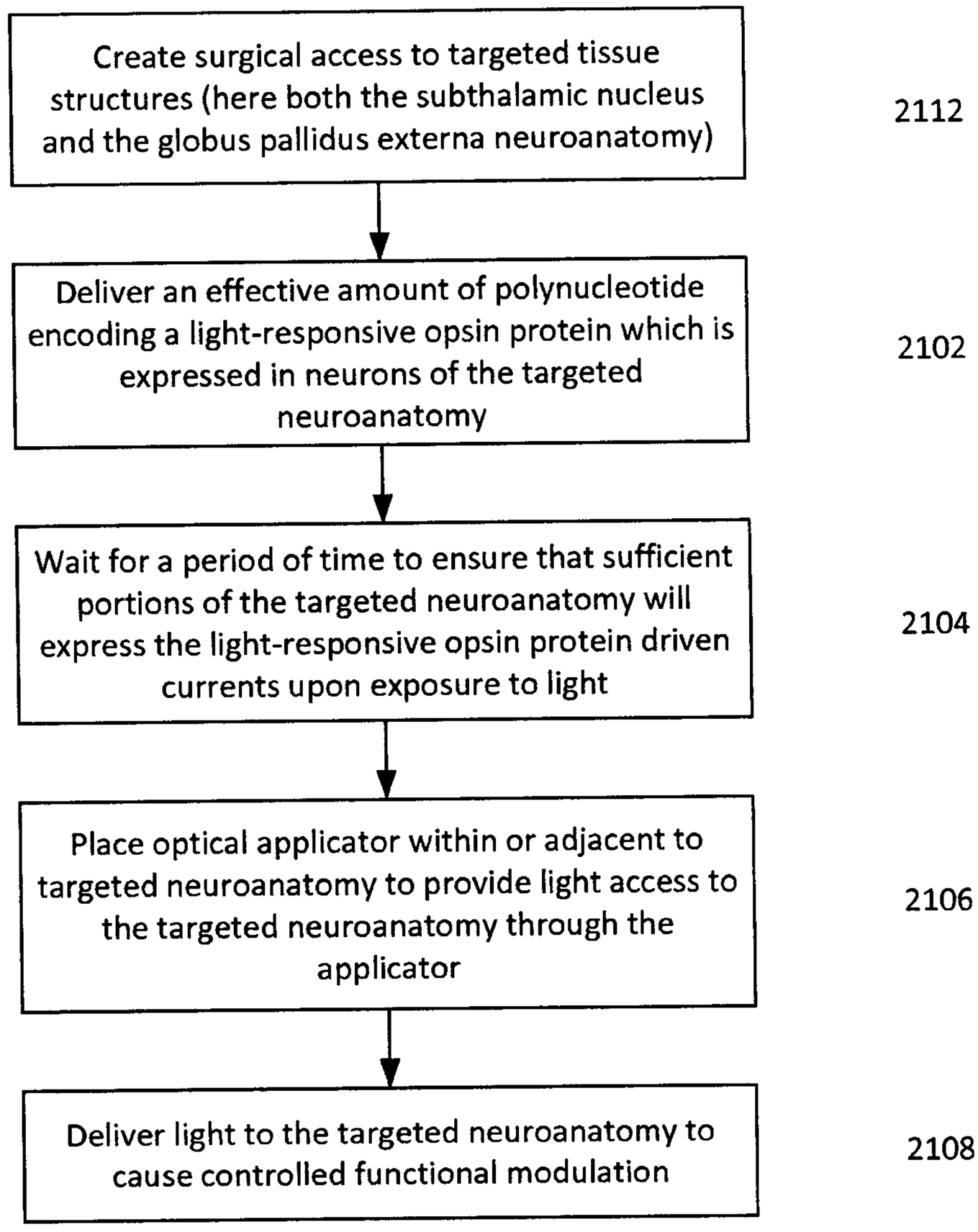

Create surgical access to targeted tissue structures (here both the subthalamic nucleus and the globus pallidus externa neuroanatomy)
2112
Deliver an effective amount of polynucleotide encoding a light-responsive opsin protein which is expressed in neurons of the targeted neuroanatomy
2102
Wait for a period of time to ensure that sufficient portions of the targeted neuroanatomy will express the light-responsive opsin protein driven currents upon exposure to light
2104
Place optical applicator within or adjacent to targeted neuroanatomy to provide light access to the targeted neuroanatomy through the applicator
2106
Deliver light to the targeted neuroanatomy to cause controlled functional modulation
2108

Figure 74

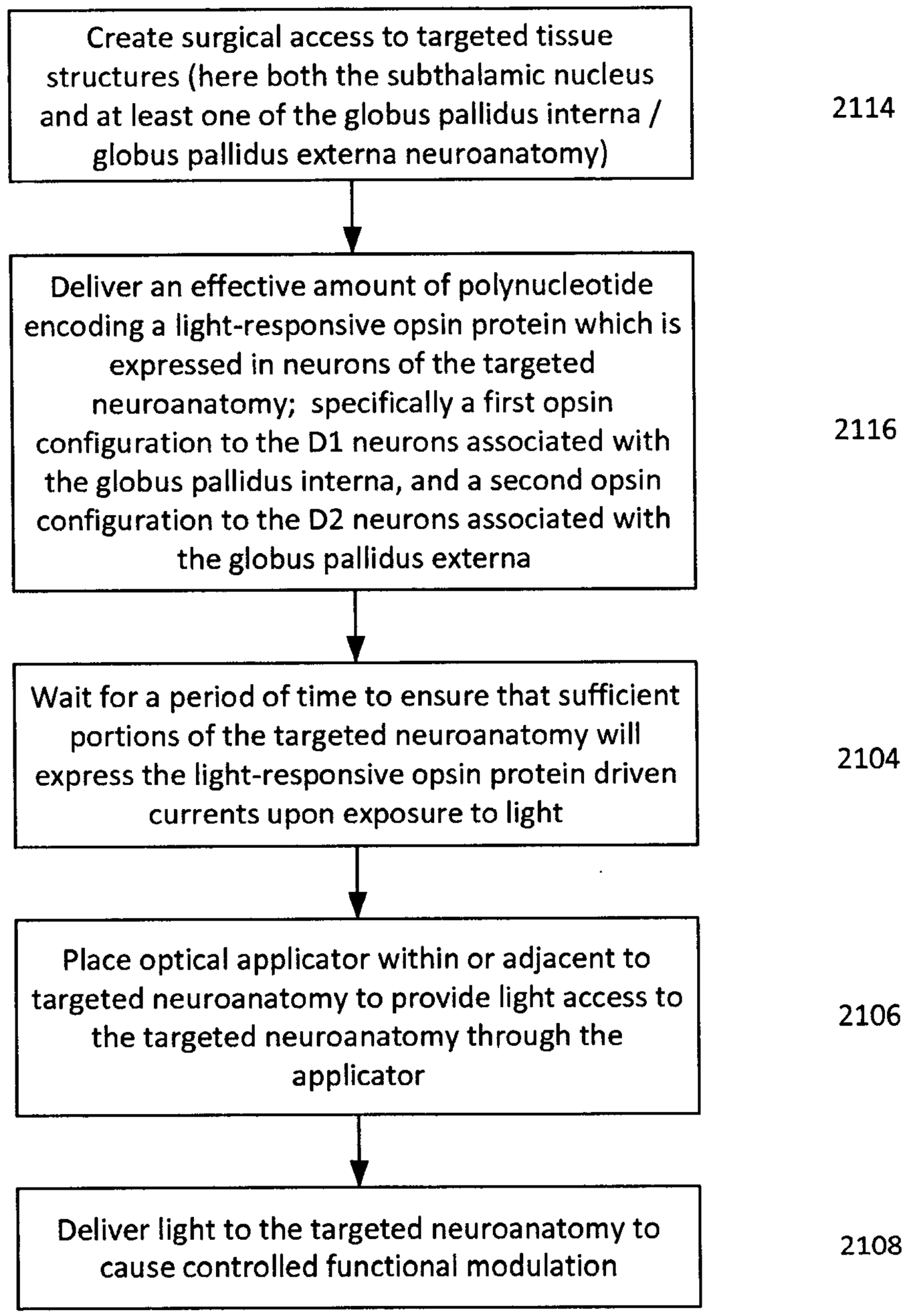

Create surgical access to targeted tissue structures (here both the subthalamic nucleus and at least one of the globus pallidus interna / globus pallidus externa neuroanatomy)
2114
Deliver an effective amount of polynucleotide encoding a light-responsive opsin protein which is expressed in neurons of the targeted neuroanatomy; specifically a first opsin configuration to the D1 neurons associated with the globus pallidus interna, and a second opsin configuration to the D2 neurons associated with the globus pallidus externa
2116
Wait for a period of time to ensure that sufficient portions of the targeted neuroanatomy will express the light-responsive opsin protein driven currents upon exposure to light
2104
Place optical applicator within or adjacent to targeted neuroanatomy to provide light access to the targeted neuroanatomy through the applicator
2106
Deliver light to the targeted neuroanatomy to cause controlled functional modulation
2108

Figure 75

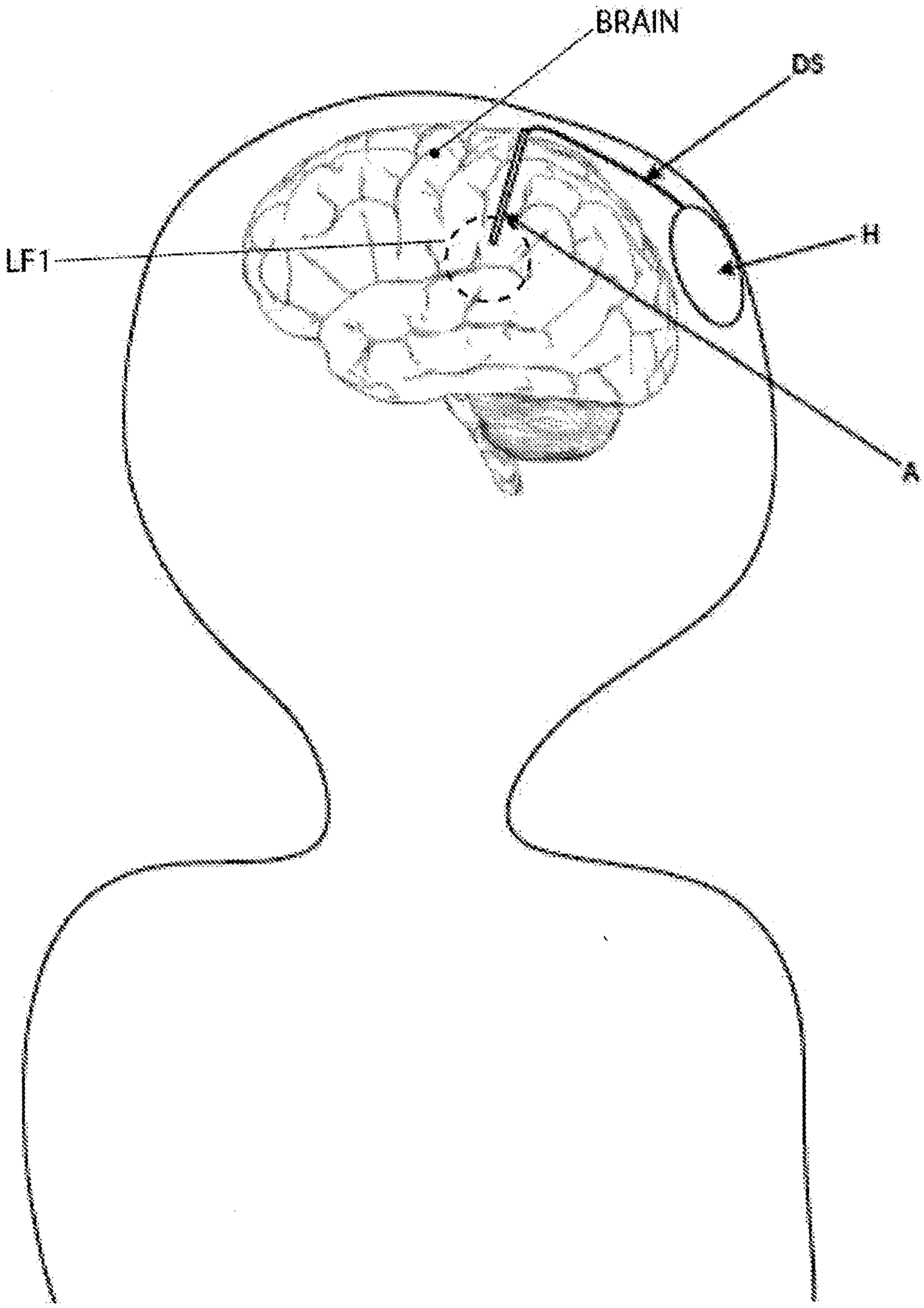


Figure 76

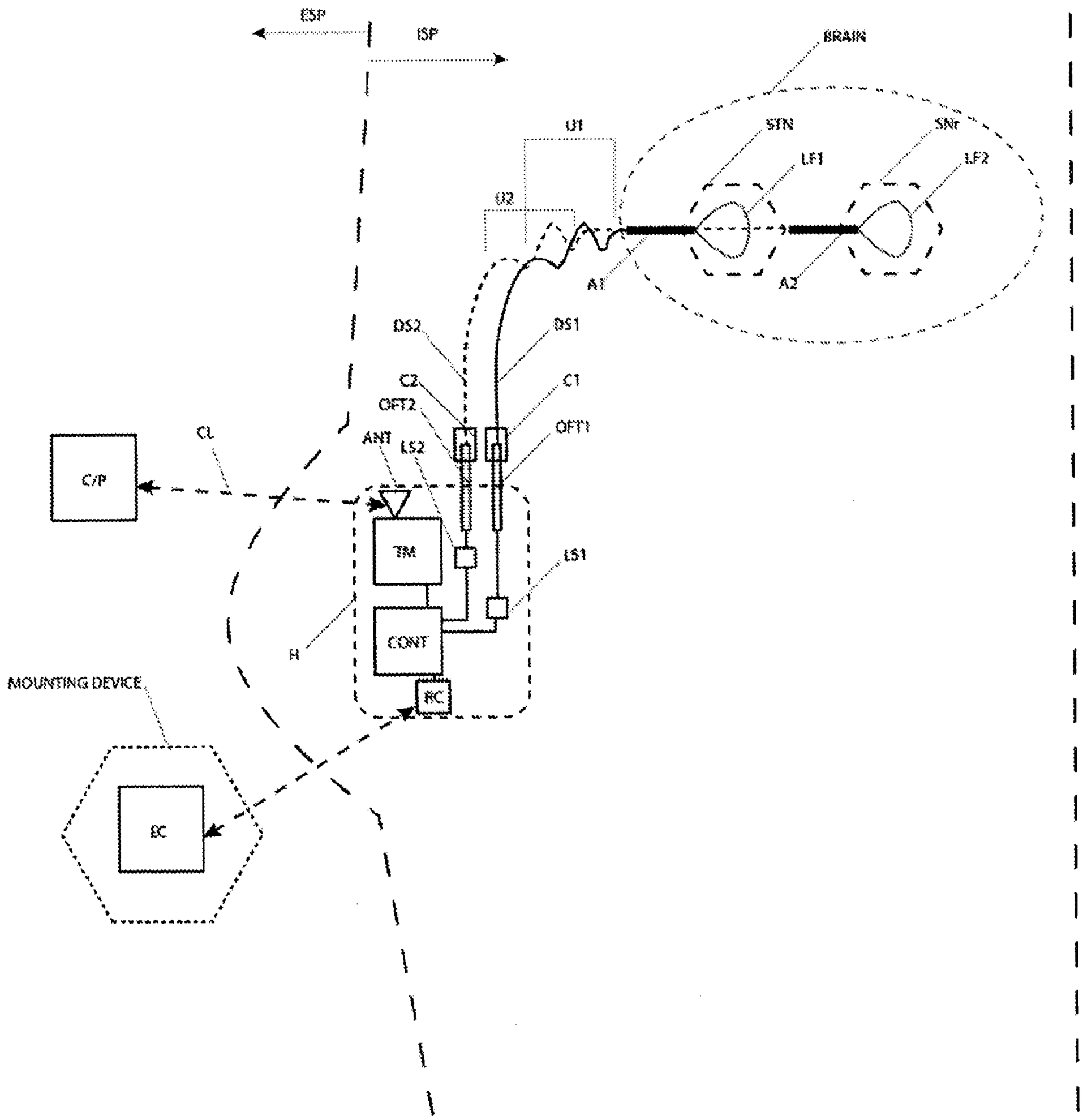

ESP
ISP
BRAIN
U1
U2
STN
SNr
LF1
LF2
A1
A2
DS2
DS1
C2
C1
OFT2
OFT1
ANT
LS2
CL
C/P
TM
LS1
CONT
H
RC
MOUNTING DEVICE
RC

Figure 77

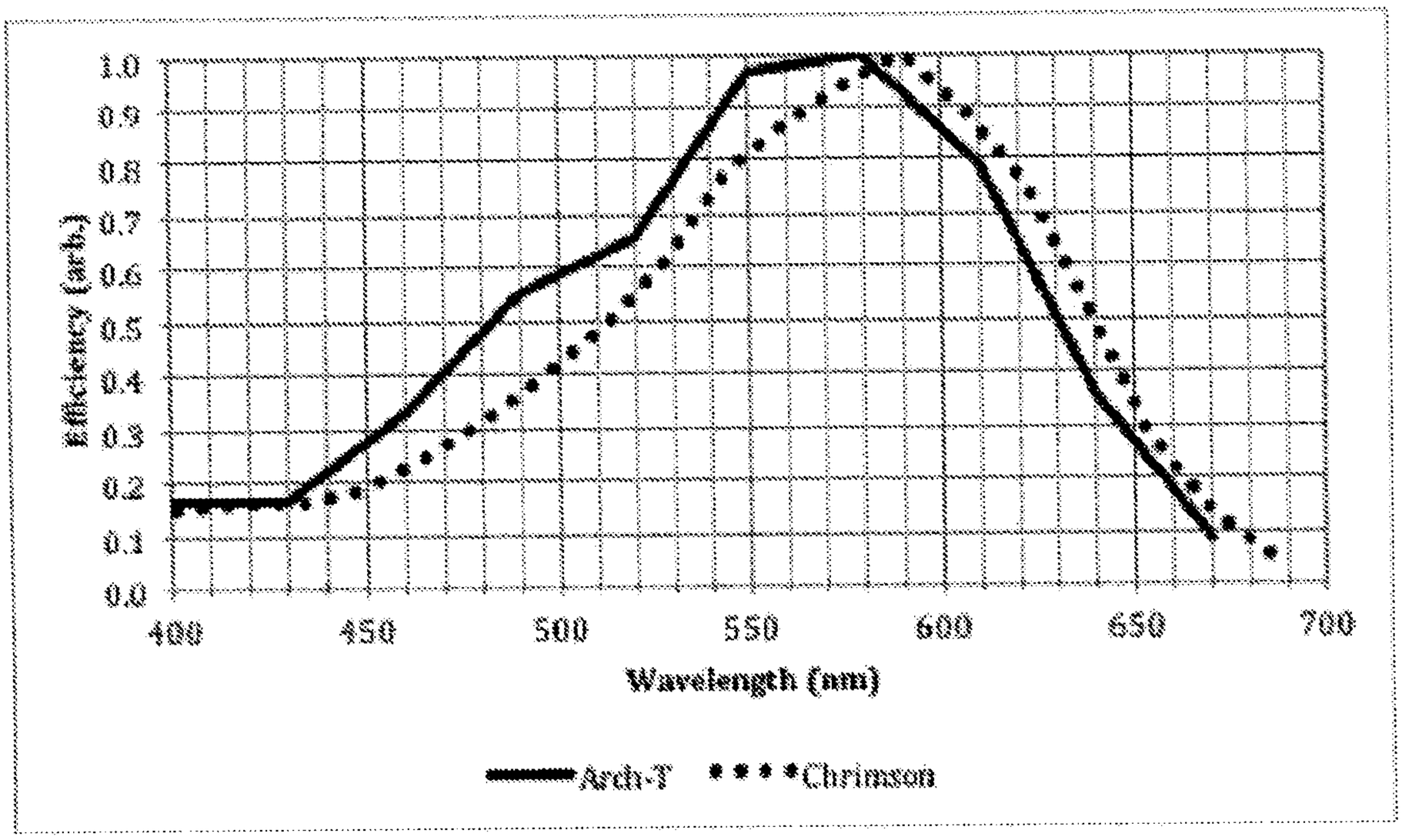
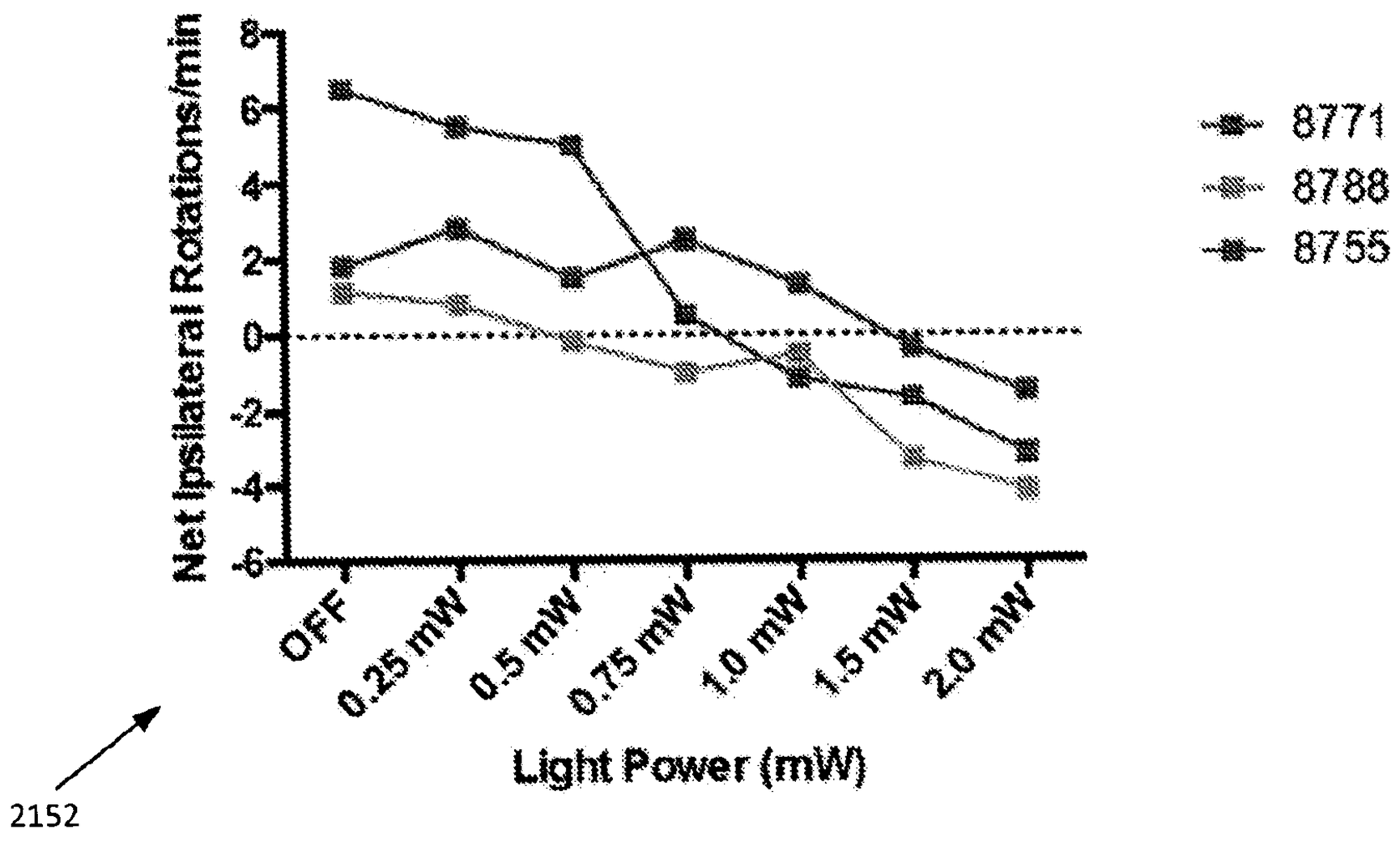


Figure 78

2150



2152

Figure 79

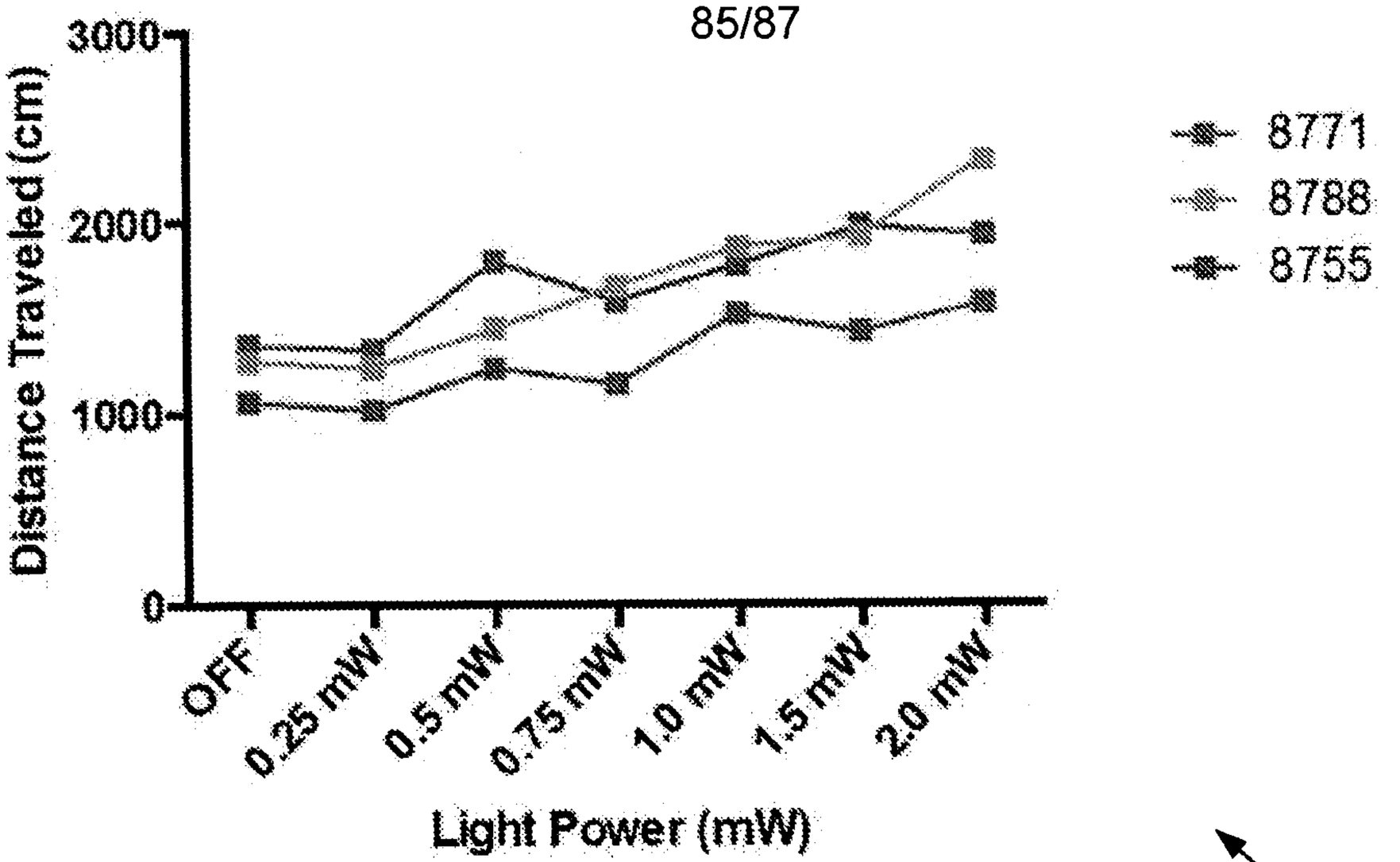


Figure 80

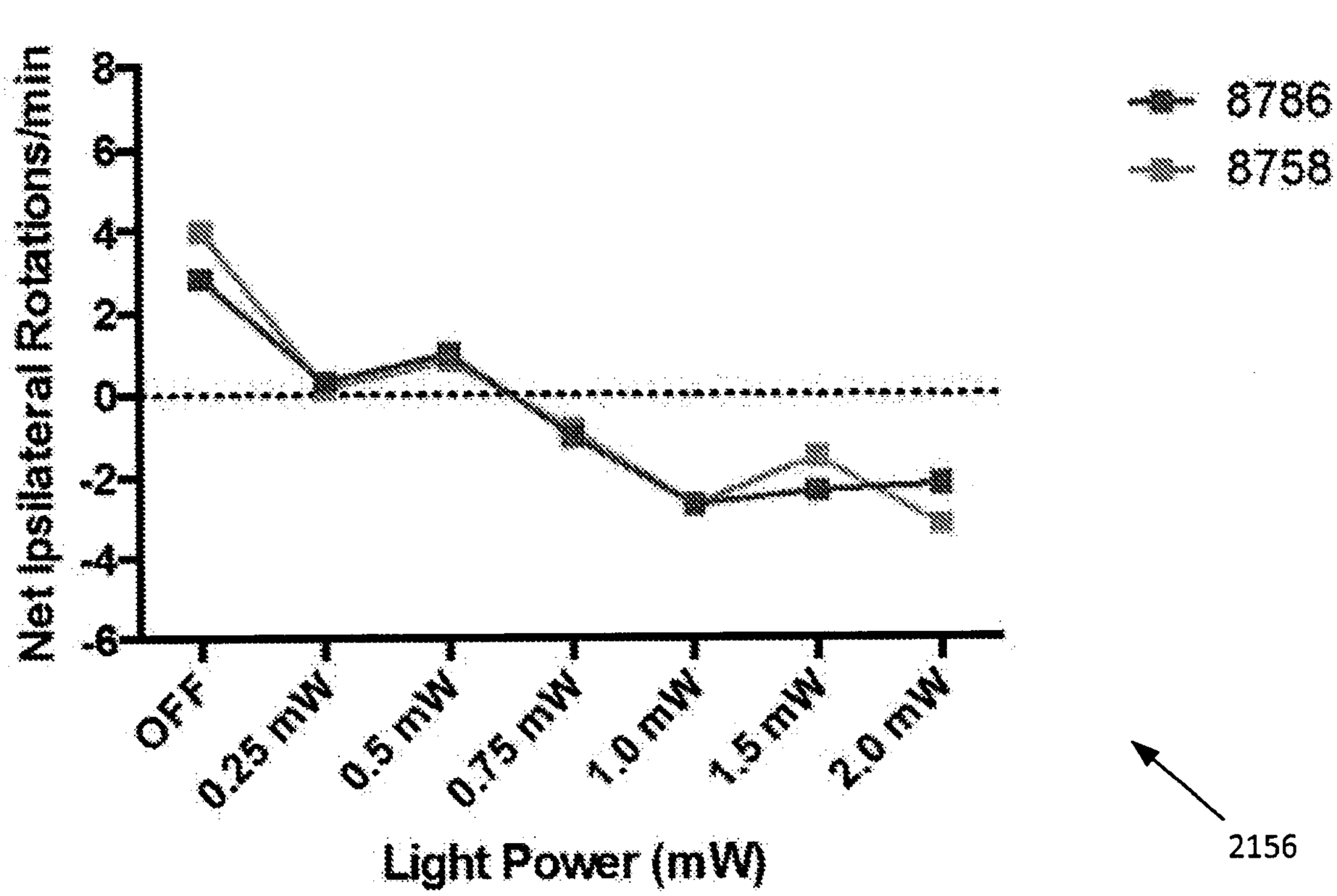


Figure 81

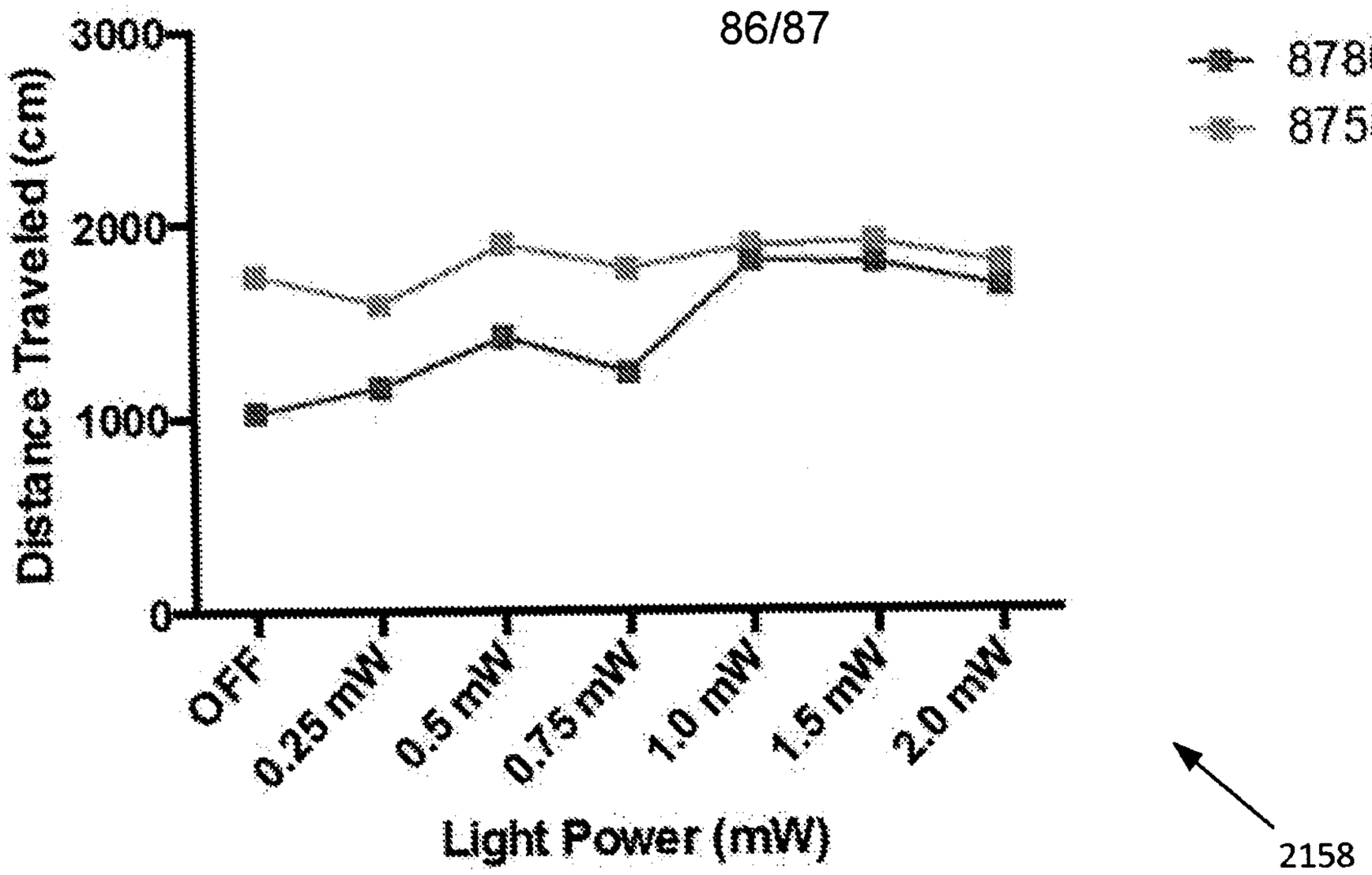


Figure 82

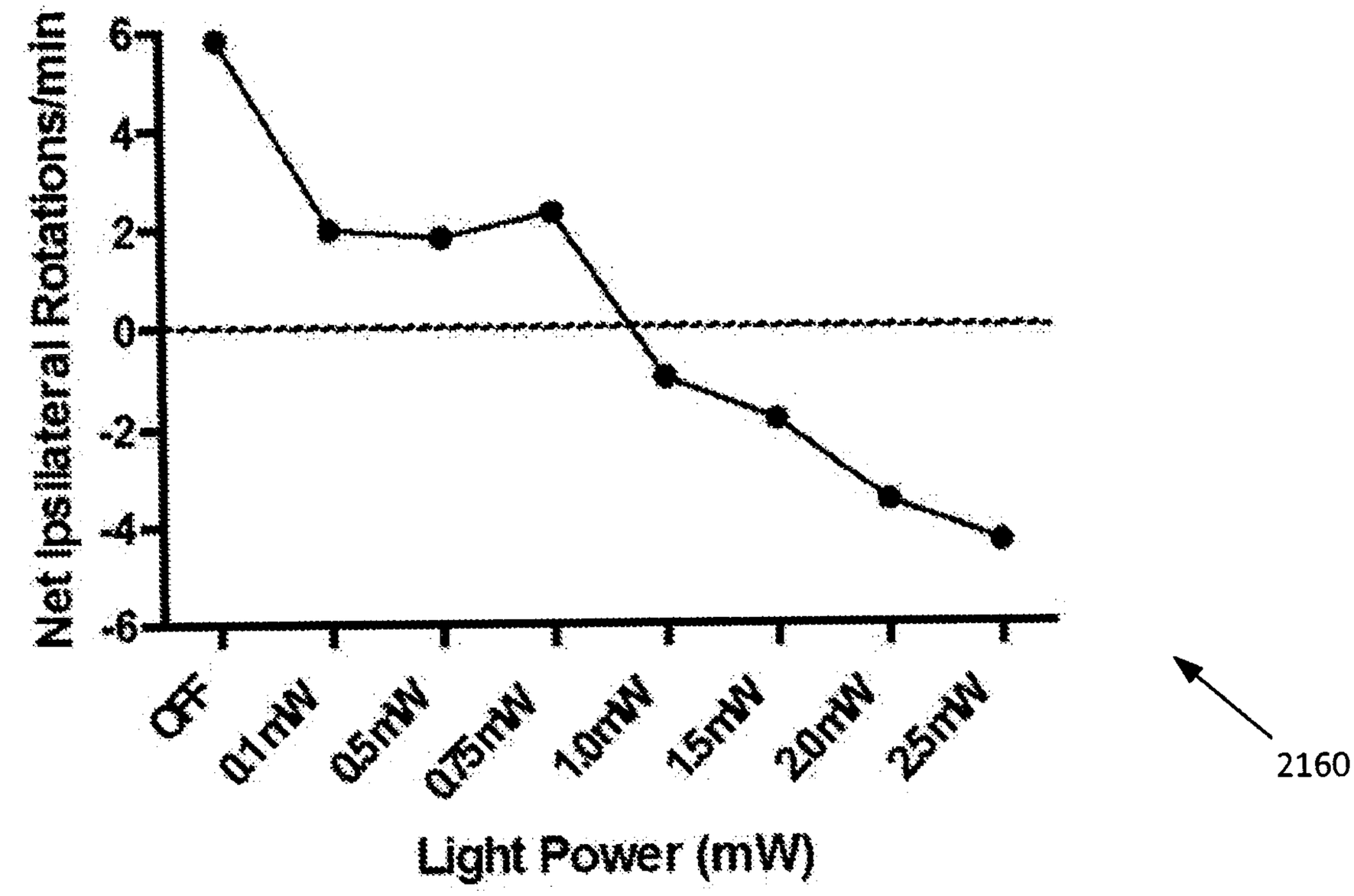


Figure 83

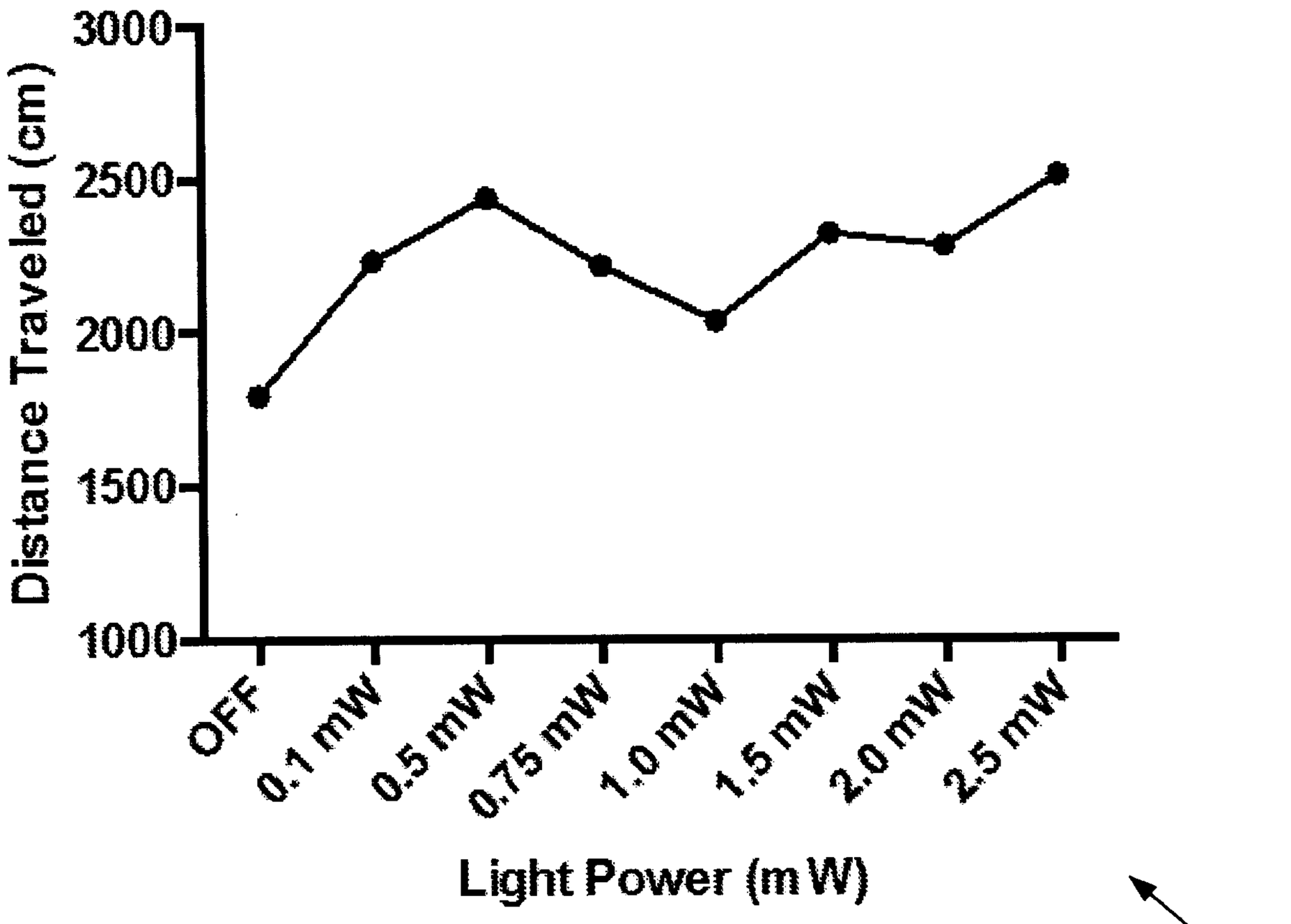

Distance Traveled (cm)
3000
2500
2000
1500
1000
OFF
0.1 mW
0.5 mW
0.75 mW
1.0 mW
1.5 mW
2.0 mW
2.5 mW
Light Power (mW)
2162

Figure 84

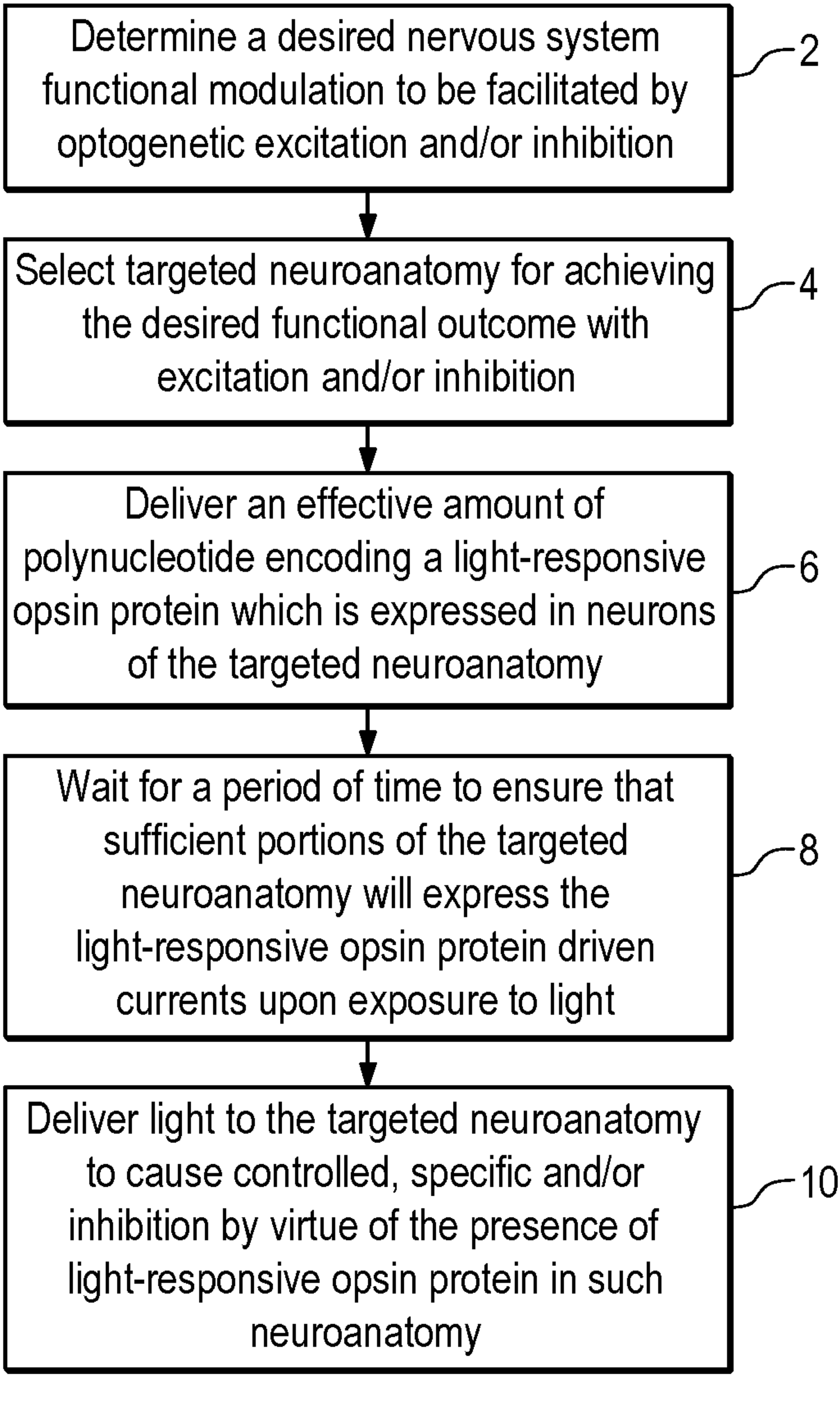

Determine a desired nervous system functional modulation to be facilitated by optogenetic excitation and/or inhibition
2
Select targeted neuroanatomy for achieving the desired functional outcome with excitation and/or inhibition
4
Deliver an effective amount of polynucleotide encoding a light-responsive opsin protein which is expressed in neurons of the targeted neuroanatomy
6
Wait for a period of time to ensure that sufficient portions of the targeted neuroanatomy will express the light-responsive opsin protein driven currents upon exposure to light
8
Deliver light to the targeted neuroanatomy to cause controlled, specific and/or inhibition by virtue of the presence of light-responsive opsin protein in such neuroanatomy
10

FIG. 1