METHODS, SYSTEMS AND DEVICES FOR OPTICAL STIMULATION OF TARGET CELLS USING AN OPTICAL TRANSMISSION ELEMENT

Related Patent Documents

This patent document claims the benefit, under 35 U.S.C. § 119(e), of U.S. Provisional Patent Application Serial No. 61/132,162 filed on June 17, 2008, which is fully incorporated herein by reference.

This application also relates to U.S. Patent Application Serial No. 11/651,422, filed January 9, 2007 (STFD.150PA), which is a continuation-in-part of U.S. Patent Application No. 11/459,636 filed on July 24, 2006 and entitled "Light-Activated Cation Channel and Uses Thereof," and to U.S. Provisional Application No. 60/701,799 filed July 22, 2005. Each of these patent documents is incorporated by reference in its entirety.

Field of the Invention

The present invention relates generally to systems and approaches for stimulating target cells, and more particularly to using optics to stimulate the target cells using an optical transmission element.

Background

The stimulation of various cells of the body has been used to produce a number of beneficial effects. One method of stimulation involves the use of electrodes to introduce an externally generated signal into cells. One problem faced by electrode-based brain stimulation techniques is the distributed nature of neurons responsible for a given mental process. Conversely, different types of neurons reside close to one another such that only certain cells in a given region of the brain are activated while performing a specific task. Alternatively stated, not only do heterogeneous nerve tracts move in parallel through tight spatial confines, but the cell bodies themselves may exist in mixed, sparsely embedded configurations. This distributed manner of processing seems to defy the best attempts to understand canonical order within the central nervous system (CNS), and makes neuromodulation a difficult therapeutic endeavor. This architecture of the brain poses a problem for electrode-based stimulation because electrodes are relatively indiscriminate with regards to the underlying physiology of the neurons that they stimulate. Instead, physical proximity of the electrode poles to the neuron is often the single largest

determining factor as to which neurons will be stimulated. Accordingly, it is generally not feasible to absolutely restrict stimulation to a single class of neuron using electrodes.

Another issue with the use of electrodes for stimulation is that because electrode placement dictates which neurons will be stimulated, mechanical stability is frequently inadequate, and results in lead migration of the electrodes from the targeted area. Moreover, after a period of time within the body, electrode leads frequently become encapsulated with glial cells, raising the effective electrical resistance of the electrodes, and hence the electrical power delivery required to reach targeted cells. Compensatory increases in voltage, frequency or pulse width, however, may spread the electrical current and increase the unintended stimulation of additional cells.

Another method of stimulus uses photosensitive bio-molecular structures to stimulate target cells in response to light. For instance, light activated proteins can be used to control the flow of ions through cell membranes. By facilitating or inhibiting the flow of positive or negative ions through cell membranes, the cell can be briefly depolarized, depolarized and maintained in that state, or hyperpolarized. Neurons are an example of a type of cell that uses the electrical currents created by depolarization to generate communication signals (*i.e.*, nerve impulses). Other electrically excitable cells include skeletal muscle, cardiac muscle, and endocrine cells. Neurons use rapid depolarization to transmit signals throughout the body and for various purposes, such as motor control (*e.g.,* muscle contractions), sensory responses (*e.g.,* touch, hearing, and other senses) and computational functions (*e.g.,* brain functions). Thus, the control of the depolarization of cells can be beneficial for a number of different purposes, including (but not limited to) psychological therapy, muscle control and sensory functions.

Optical-based stimulus, however, often involves the generation of heat which can be passed to cells of the body. Heat affects both the function and the physical viability of many cell types and may cause cell damage or death. In brain tissue, for example, the threshold for cell death is generally about fifty-six degrees Celsius maintained for one second, or fifty-two degrees for longer periods of time. Tissues held above forty-three degrees Celsius for more than an hour or so may have their physiological processes (including cell division) interrupted. Even more subtle elevations in temperature, above the normal thirty-seven degrees Celsius, are thought to change metabolic processes including affecting spontaneous firing rate.

Summary

The claimed invention is directed to photosensitive bio-molecular structures and related methods. The present invention is exemplified in a number of implementations and applications, some of which are summarized below.

An embodiment of the present invention is directed towards an optical delivery device for delivering light to a patient. The device includes a light source for producing light from electrical power. An optical transmission element is made from a material that is substantially transparent to the light from the light source. This transmission element substantially encases the light source at a proximal end. The transmission element delivers light from the light source to a distal end. The shape and size of the transmission element facilitates implanting of the element within a patient. A fixation portion physically couples to the optical transmission element and secures the device to the patient. A heat dissipation portion removes heat from the near optical transmission element and the light source and dissipates the removed heat through the fixation portion.

Consistent with an embodiment of the present invention, a method is implemented stimulating target cells *in vivo*. Light-activated ion channels are engineered in one or more *in vivo* target cells. A device is surgically implanted. The device includes a light source for producing light from electrical power, an optical transmission element made from a material that is substantially transparent to the light from the light source, the material having an elongated shape that substantially encases the light source at a proximal end and that is for delivering the light from the light source to a distal end, a fixation portion physically coupled to the optical transmission element for attachment to the patient, and a heat dissipation portion to remove heat from near the optical coupling of the optical transmission element and the light source and to dissipate the removed heat through the fixation portion. After implantation, the light source is activated to stimulate the target cells.

According to one example embodiment of the present invention, an implantable arrangement is implemented having a light-generation device for generating light. The arrangement also has a biological portion that modifies target cells for stimulation in response to light generated by the light-generation means *in vivo*. Stimulation may be manifested as either upregulation (*e.g.*, increased neuronal firing activity), or

downregulation (*e.g.,* neuronal hyperpolarization, or alternatively, chronic depolarization) of activity at the target.

According to another example embodiment of the present invention, a method is implemented for stimulating target cells using photosensitive proteins that bind with the target cells. The method includes a step of implanting the photosensitive proteins and a light generating device near the target cells. The light generating device is activated and the photosensitive protein stimulates the target cells in response to the generated light.

Applications include those associated with any population of electrically-excitable cells, including neurons, skeletal, cardiac, and smooth muscle cells, and insulin-secreting pancreatic beta cells. Major diseases with altered excitation-effector coupling include heart failure, muscular dystrophies, diabetes, pain, cerebral palsy, paralysis, depression, and schizophrenia. Accordingly, the present invention has utility in the treatment of a wide spectrum of medical conditions, from Parkinson's disease and brain injuries to cardiac dysrhthmias, to diabetes, and muscle spasm.

According to other example embodiments of the present invention, methods for generating an inhibitory neuron-current flow involve, in a neuron, engineering a protein that responds to light by producing an inhibitory current to dissuade depolarization of the neuron. In one such method, the protein is halorhodopsin-based and in another method the protein is an inhibitory protein that uses an endogenous cofactor.

According to another example embodiment of the present invention, a method for controlling action potential of a neuron involves the following step: engineering a first light responsive protein in the neuron; producing, in response to light, an inhibitory current in the neuron and from the first light responsive protein; engineering a second light responsive protein in the neuron; and producing, in response to light, an excitation current in the neuron from the second light responsive protein.

In another method for controlling a voltage level across a cell membrane of a cell, the method comprises: engineering a first light responsive protein in the cell; measuring the voltage level across the cell membrane; and producing, in response to light of a first wavelength and using the first light responsive protein, a current across the cell membrane that is responsive to the measured voltage level.

The above summary of the present invention is not intended to describe each illustrated embodiment or every implementation of the present invention. The figures and detailed description that follow more particularly exemplify these embodiments.

Brief Description of the Drawings

The invention may be more completely understood in consideration of the detailed description of various embodiments of the invention that follows in connection with the accompanying drawings, in which:

FIG. 1A depicts an implantable device as implemented for deep-brain neuromodulation, consistent with an embodiment of the present invention;

FIG. 1B illustrates a detailed view of a possible implantation orientation and location, consistent with embodiments of the present invention;

FIG. 2A depicts an elongate structure integrally coupled to an LED element for efficiently delivering light to a target location, consistent with an embodiment of the present invention;

FIG. 2B depicts an embodiment of the present invention in which elongate structure is integrally formed to the electronic portions;

FIG. 2C illustrates an embodiment of the present invention in which, at the proximal end of the device, a heat sink/mounting base surrounds a negative lead and a positive lead;

FIGs. 3A and 3B depict an elongate structure for controlling light by rotational movement of the elongate structure, consistent with an embodiment of the present invention;

FIGs. 3C and 3D show movement of a light delivery structure within a fixation portion, consistent with an embodiment of the present invention; and

FIG. 4 shows a light delivery structure, consistent with an embodiment of the present invention.

While the invention is amenable to various modifications and alternative forms, specifics thereof have been shown by way of example in the drawings and will be described in detail. It should be understood, however, that the intention is not to limit the invention to the particular embodiments described. On the contrary, the intention is to cover all modifications, equivalents, and alternatives falling within the spirit and scope of the invention.

Detailed Description

The present invention is believed to be useful for facilitating practical application of a variety of photosensitive bio-molecular structures, and the invention has been found to be particularly suited for use in arrangements and methods dealing with cellular membrane voltage control and stimulation, including those using an optical transmission element designed for implantation. While the present invention is not necessarily limited to such applications, various aspects of the invention may be appreciated through a discussion of various examples using this context.

An embodiment of the present invention is directed towards an optical delivery device for delivering light to a patient. The device includes a light source for producing light from electrical power. An optical transmission element is made from a material that is substantially transparent to the light from the light source. This transmission element substantially encases the light source at a proximal end. The transmission element delivers light from the light source to a distal end. The shape and size of the transmission element facilitates implanting of the element within a patient. A fixation portion physically couples to the optical transmission element and secures the device to the patient. A heat dissipation portion removes heat from the near optical transmission element and the light source and dissipates the removed heat through the fixation portion.

Another embodiment of the present invention is directed toward a transmission element is made from a material that is substantially transparent to the light from the light source. This transmission element substantially encases the light source at a proximal end. The transmission element delivers light from the light source to a distal end. The shape and size of the transmission element facilitates implanting of the element within a patient. In certain implementations, the transmission element can be designed for fixation to the person or animal under test/treatment.

Light can be delivered to targeted locations by optical fiber carrying light from an external source, or by implanted light-emitting diode (LED). An optical fiber approach to optogenetic stimulation, is well-suited to precise, deep-brain implantation, as the cylindrical shape and narrow-diameter (for example 20 microns) permit stereotactic insertion with minimal trauma to tissue, while assuring focused delivery of light at the end of the fiber. Such an optical fiber approach uses a bulky, high-power-consumption, heat-generating light source (for example a Xenon lamp with an optical coupling to the fiber). Heat is generated not only by the light generation process, but also by the optical

coupling, *e.g.*, where light that fails to cross the interfaces of different components along the light path generates heat. Yet other potential heat sources are electrical circuit elements, which can provide control of the light source.

LED approaches to optogenetic stimulation, while often more compact (in total) and more power efficient than a Xenon lamp with optical fiber coupling, are often less compact at the point of light output, and also generate significant heat close to the source of the output. Additionally, conventional LEDs lack the smooth linear configuration that lends optical fiber implantation to the stereotactic surgical approach. Thus, the implantation of LEDs can be more intrusive and physically damaging to tissues. LEDs may be optically coupled to optical fibers and thereby physically displacing the principal area of heat generation, and the principal area of light delivery. However, the light coupling process between the LED and optical fiber is inefficient, causing substantial heat loss due to the reflective and refractive properties of the interfaces between LED lens and optical fiber.

Accordingly, specific implementations can be particularly useful for mitigating unwanted heat from an implanted light source. One such implementation involves an optical delivery device that provides efficient opto-coupling between a relatively low-power optical source and a transmission element designed for implantation and delivery of light to target cells. The transmission element is designed to provide total internal reflection of light when implanted within a patient. Total internal reflection occurs when the angle of incidence of the light is sufficient relative to the critical angle above which reflection occurs.

In an embodiment of the present invention, the transmission element is designed to be maintained in a relatively rigid or unbending physical shape. This can be particularly useful for designing the transmission element with respect to the total internal reflection of light when implanted within a patient. For instance, fiber optic cable is often specifically designed to allow for a maximum bending angle. This bending angle is determined as a function of the optical properties of the core and the surrounding cladding. Reducing or eliminating such bending from the transmission element relaxes the design constraints, *e.g.*, by effectively increasing the range of acceptable angles of incidence of the light.

Some implementations use a transmission element that has a desired critical angle that is defined by an interface between the transmission element and properties of internal

body components such as body fluids or tissue. In this manner, the internal body components function like an external cladding-type layer during the delivery of light to a target location.

Embodiments of the present invention relate to the design of the transmission element. A variety of different shapes are possible for the shaft of the transmission element, *e.g.*, cylindrical, conical or flat/rectangular. Moreover, the end of the transmission element for placement near the target location can be designed to further control the delivery of light. This can include, for instance, focusing light toward a tightly controlled area or dispersing light over a large area.

Aspects of the present invention also relate to methods and devices for heat dissipation. For instance, a heat-conductive section can be thermally coupled to sources of heat. The sources of heat may include the optical light source, control electronics, power source or external temperature source, such as environmental sources of heat. The heat-conductive section can be designed to dissipate heat away from the insertion point of the transmission element. This can include dissipation of heat into the air, the vascularized bone and/or soft tissue. Thermally-insulating material can be placed between the thermally-conductive (heat-sink) section and the insertion point, thereby mitigating heating of internal tissue.

The heat-conductive section can be designed with sufficient surface area to dissipate the required amount of heat. The heat-conductive section can be designed from a number of different conductive materials including, but not limited to, thermally-conductive metals like copper. The surface area of the heat-conductive section can be designed with porous material, fins or other aspects that help increase the surface area. In a particular implementation, the heat-conductive section is insulated from external environmental heat sources. The heat is thereby substantially all dissipated into the vascularized bone and/or soft tissue. This can be particularly useful for allowing use of the device in varying environments and external temperatures.

According to one embodiment of the present invention, a thermal sensor is used to monitor the temperature near the insertion point. In response to the temperature reading, the device can emit a warning signal and/or modify operation of the light source. For instance, the device can disable the light source in response to the temperature exceeding a predetermined threshold level.

In some embodiments of the present invention, a control circuit and a power source are included as components of the device. These components can be designed for external placement on the patient. For instance, a battery and microcontroller is placed within, or as part of, a mounting base that is affixed to the patient, *e.g.*, to the skull for neural stimulation. In certain implementations, one or more of these components are placed away from the insertion point. Electrical connections provide control over the light source. Thermal-insulation can be introduced between these components and the insertion point to mitigate heat transfer to the insertion point.

In certain implementations involving a rigid transmission element, the transmission element has a set length that corresponds to an approximate insertion depth for delivery of light to a target location. Each patient, however, can have a different morphology and/or desired target location. In one instance, the transmission element can be individually modified for each procedure. This can be accomplished by removing a section of the transmission element to obtain the desired length. In another implementation, an adjustable portion of the mounting base allows for control of the depth of the transmission element.

Certain embodiments of the present invention relate to allowed movement of the transmission element relative to the mounting base of the system. For instance, the mounting base allows the transmission element to freely move in a lateral direction. Once the transmission element is properly located, the mounting base secures the transmission element to prevent future movement. The transmission element is secured using a clamping mechanism, a cementing agent or other suitable fixation mechanisms. Another potential use of allowed movement of the transmission element relative to the mounting base of the system relates to further control of the light delivery location. The tip of the transmission element can be designed to direct light at an angle relative to the long-axis of the transmission element. By allowing rotational movement of such a transmission element, the light-stimulus location can be adjusted. Once the desired orientation is determined, *e.g.*, by testing the effectiveness of various orientations, the transmission element can be fixed to prevent further movement.

While not so limited, embodiments of the present invention are particularly well-suited for use with one or more of the following example embodiments directed towards light responsive proteins.

Consistent with one example embodiment of the present invention, a light-responsive protein is engineered in a cell. The protein affects a flow of ions across the cell membrane in response to light. This change in ion flow creates a corresponding change in the electrical properties of the cells including, for example, the voltage and current flow across the cell membrane. In one instance, the protein functions *in vivo* using an endogenous cofactor to modify ion flow across the cell membrane. In another instance, the protein changes the voltage across the cell membrane so as to dissuade action potential firing in the cell. In yet another instance, the protein is capable of changing the electrical properties of the cell within several milliseconds of the light being introduced. For further details on delivery of such proteins, reference may be made to U.S. Patent Application No. 11/459,636 filed on July 24, 2006 and entitled "Light-Activated Cation Channel and Uses Thereof", which is fully incorporated herein by reference.

Consistent with a more specific example embodiment of the present invention a protein, NpHR, from *Natronomonas pharaonis* is used for temporally-precise optical inhibition of neural activity. NpHR allows for selective inhibition of single action potentials within rapid spike trains and sustained blockade of spiking over many minutes. The action spectrum of NpHR is strongly red-shifted relative to ChR2 but operates at similar light power, and NpHR functions in mammals without exogenous cofactors. In one instance, both NpHR and ChR2 can be expressed in the target cells. Likewise, NpHR and ChR2 can be targeted to *C. elegans* muscle and cholinergic motoneurons to control locomotion bidirectionally. In this regard, NpHR and ChR2 form an optogenetic system for multimodal, high-speed, genetically-targeted, all-optical interrogation of living neural circuits.

Certain aspects of the present invention are based on the identification and development of an archaeal light-driven chloride pump, such as halorhodopsin (NpHR), from Natronomonas pharaonis, for temporally-precise optical inhibition of neural activity. The pump allows both knockout of single action potentials within rapid spike trains and sustained blockade of spiking over many minutes, and it operates at similar light power compared to ChR2 but with a strongly red-shifted action spectrum. The NpHR pump also functions in mammals without exogenous cofactors.

According to other example embodiments of the present invention, methods for generating an inhibitory neuron-current flow involve, in a neuron, engineering a protein

that responds to light by producing an inhibitory current to dissuade depolarization of the neuron. In one such method, the protein is halorhodopsin-based and in another method the protein is an inhibitory protein that uses an endogenous cofactor.

In another example embodiment, a method for controlling action potential of a neuron involves the following steps: engineering a first light responsive protein in the neuron; producing, in response to light, an inhibitory current in the neuron and from the first light responsive protein; engineering a second light responsive protein in the neuron; and producing, in response to light, an excitation current in the neuron from the second light responsive protein.

In another method for controlling a voltage level across a cell membrane of a cell, the method includes: engineering a first light responsive protein in the cell; measuring or inferring the voltage level across the cell membrane (*e.g.*, using voltage sensitive dyes or measurements of brain activity); and producing, in response to light of a first wavelength and using the first light responsive protein, a current across the cell membrane that is responsive to the measured or inferred voltage level.

Another aspect of the present invention is directed to a system for controlling an action potential of a neuron *in vivo*. The system includes a delivery device, a light source, and a control device. The delivery device introduces a light responsive protein to the neuron, with the light responsive protein producing an inhibitory current. The light source generates light for stimulating the light responsive protein, and the control device controls the generation of light by the light source.

In more detailed embodiments, such a system is further adapted such that the delivery device introduces the light responsive protein by one of transfection, transduction and microinjection, and/or such that the light source introduces light to the neuron via one of an implantable light generator and fiber-optics.

Another aspect of the present invention is directed to a method for treatment of a disorder. The method targets a group of neurons associated with the disorder; and in this group, the method includes engineering an inhibitory proteins that use an endogenous cofactor to respond to light by producing an inhibitory current to dissuade depolarization of the neurons, and exposing the neurons to light, thereby dissuading depolarization of the neurons.

According to yet another aspect of the present invention is directed to identifying and developing an archaeal light-driven chloride pump, such as halorhodopsin (NpHR),

from Natronomonas pharaonis, for temporally-precise optical inhibition of neural activity. The pump allows both knockout of single action potentials within rapid spike trains and sustained blockade of spiking over many minutes, and it operates at similar light power compared to ChR2 but with a strongly red-shifted action spectrum. The NpHR pump also functions in mammals without exogenous cofactors.

More detailed embodiments expand on such techniques. For instance, another aspect of the present invention co-expresses NpHR and ChR2 in the species (*e.g.*, a person or a mouse). Also, NpHR and ChR2 are integrated with calcium imaging in acute mammalian brain slices for bidirectional optical modulation and readout of neural activity. Likewise, NpHR and ChR2 can be targeted to *C. elegans* muscle and cholinergic motoneurons to control locomotion bidirectionally. Together NpHR and ChR2 can be used as a complete and complementary opto-genetic system for multimodal, high-speed, genetically-targeted, all-optical interrogation of living neural circuits.

In addition to NpHR and ChR2, there are a number of channelrhodopsins, halorhodopsins, and microbial opsins that can be engineered to optically regulate ion flux or second messengers within cells. Various embodiments of the invention include codon-optimized, mutated, truncated, fusion proteins, targeted versions, or otherwise modified versions of such ion optical regulators. Thus, ChR2 and NpHR (*e.g.*, GenBank accession number is EF474018 for the 'mammalianized' NpHR sequence and EF474017 for the 'mammalianized' ChR2(1-315) sequence) are used as representative of a number of different embodiments. Discussions specifically identifying ChR2 and NpHR are not meant to limit the invention to such specific examples of optical regulators. For further details regarding the above mentioned sequences reference can be made to "Multimodal fast optical interrogation of neural circuitry" by Feng Zhang, *et al*, Nature (April 5, 2007) Vol. 446: pp. 633-639, which is fully incorporated herein by reference.

Consistent with a particular embodiment of the present invention, a protein is introduced to one or more target cells. When introduced into a cell, the protein changes the potential of the cell in response to light having a certain frequency. This may result in a change in resting potential that can be used to control (dissuade) action potential firing. In a specific example, the protein is a halorhodopsin that acts as a membrane pump for transferring charge across the cell membrane in response to light. Membrane pumps are energy transducers which use electromagnetic or chemical bond energy for translocation of specific ions across the membrane. For further information regarding halorhodopsin

membrane pumps reference can be made to "Halorhodopsin Is a Light-driven Chloride Pump" by Brigitte Schobert, *et al*, The Journal of Biological Chemistry Vol. 257, No. 17. September 10, 1982, pp. 10306-10313, which is fully incorporated herein by reference.

The protein dissuades firing of the action potential by moving the potential of the cell away from the action potential trigger level for the cell. In many neurons, this means that the protein increases the negative voltage seen across the cell membrane. In a specific instance, the protein acts as a chloride ion pump that actively transfers negatively charged chloride ions into the cell. In this manner, the protein generates an inhibitory current across the cell membrane. More specifically, the protein responds to light by lowering the voltage across the cell thereby decreasing the probability that an action potential or depolarization will occur.

As used herein, stimulation of a target cell is generally used to describe modification of properties of the cell. For instance, the stimulus of a target cell may result in a change in the properties of the cell membrane that can lead to the depolarization or polarization of the target cell. In a particular instance, the target cell is a neuron and the stimulus affects the transmission of impulses by facilitating or inhibiting the generation of impulses by the neuron.

Turning now to the figures, FIG. 1A depicts an implantable device as implemented for deep-brain neuromodulation, consistent with an embodiment of the present invention. FIG. 1A and the following discussion specifically mention and discuss deep-brain neuromodulation; however, the invention is not so limited. The system of FIG. 1A includes elongate transmission elements 104 and 106. Fixation bases 114 and 112 fix the transmission elements 104 and 106, respectively, to the skull of the patient 102. Light source, such as LEDs, produces light that is directed to target locations by transmission elements 104 and 106. A pulse-generator circuit 115, having a power source 116, generates control pulses that cause the LEDs to produce light.

In a specific implementation, a surgeon implants flexible power/control leads 113 and 115 under the skin. The battery 116 and pulse-generator unit 115 are implanted separately from the LEDs 104 and 106, for example against the chest wall. Heat-sink/fixation base 112 surrounds the proximal portion of LED with elongate structure 106, while heat-sink/fixation base 114 surrounds the proximal portion of LED with elongate structure 104. Implantation to sub-surface regions of the brain or body can be accomplished by pushing the device in a linear fashion from the external surface of the

body part, toward the target, typically using stereotactic devices and associated methods used for precise placement of instruments and implantable devices within the brain and body. Commercially available devices for stereotactic placement of implantable include the "Universal Tool" customization feature on the "Stealth Station" series of computerized image guidance systems by the Surgical Navigation Technologies division (Broomfield, CO) of Medtronic Inc. (Minneapolis, MN).

By integrally forming an elongate structure with the electronic elements of an LED, the device becomes readily implantable in a precise targeted manner, and is spatially fixable. The primary source of heat is physically displaced from sensitive underlying tissues such as brain cells, such that damage to cells is mitigated. For instance, the heat sink at the proximal end captures and diffuses heat into vascularized bone and soft tissue that is less heat sensitive than the target cells or interposed tissue.

FIG. 1B illustrates a detailed view of a possible implantation orientation and location, consistent with embodiments of the present invention. A light source, such as an LED, couples to an elongate structure 125, which is implanted in brain 129. Heat-sink/fixation base 140 attaches to the proximal portion of the light source and elongate structure, surrounding the point of electricity-to-light conversion. Heat-sink/fixation base 130 may be adhered to skull 132, for example with methacrylate, or sutured or otherwise affixed to tissue 133 overlying or underlying bone. The distal end of the combination of LED and elongate structure 125 is placed so as to illuminate the biological portion 127, which may be described as an anatomical target optical stimulation. In this illustration biological portion 127 is Brodmann's Area 25 of the brain. Other potential targeted biological portions depend upon the specific experimental or therapeutic application and can include, but are not limited to, the subthalamic nucleus, the globus pallidus interna, the dentate gyrus, the CA-1 field of the hippocampus, the medial hypothalamic area and the lateral hypothalamic area.

FIG. 2A depicts an elongate structure integrally coupled to an LED element for efficiently delivering light to a target location, consistent with an embodiment of the present invention. Elongate structure 210 is depicted as a cylindrical to conical, linearly-extending, optically transparent or translucent object of generally uniform internal consistency. Elongate structure 210 need not be limited to any specific materials but can be implemented using glass or plastics, such as polycarbonate. Elongate structure 210 is tightly formed to LED element 202, and the distal portions of negative electrode 206 and

positive electrode 204. Light 208 is emitted from diode 202 and traverses elongate structure 210 along light beams 212 and 214. The light beams reflect upon the surface boundaries of elongate structure 210. Assuming the angle of incidence of the light is sufficient relative to the critical angle above which reflection occurs, the light is redirected internally to the elongate structure 210. A substantial portion of the light ultimately passes out of elongate structure 210 as beams 216, which illuminate a target location 218, *e.g.*, a light-sensitive cell, in a manner that modifies its activity.

FIG. 2B depicts an embodiment of the present invention in which elongate structure 230 is integrally formed to the electronic portions, including the distal portions of positive lead 224 and negative lead 226 and interposed diode element (not shown) and thus able to efficiently deliver light to the biological portion, in this case, a neuron. Elongate structure 230 is a longitudinally tapering cylinder of optical-grade material such as glass or plastic. Blue light 228 is emitted within the proximal portion of elongate structure 230 an internally reflects. The light leaves the distal end of elongate structure 230 as blue light 236.

In a particular implementation, the target location 218 includes one or more neural cells expressing an optically responsive ion channel or pump such as ChR2. When pulses of blue light 236 falls upon ChR2-expressing neural cell 218, this cell exhibits an action potential with each pulse, and is thereby regulated by electrical input to leads 224 and 226.

FIG. 2C illustrates an embodiment of the present invention in which, at the proximal end of the device, heat sink/mounting base 262 surrounds negative lead 256 and positive lead 254. In a particular implementation, the diode element interposed between them (not shown) emits yellow light. Elongate structure 260 is a longitudinally tapering cylinder of optical-grade material such as glass or plastic, which delivers light to neuron 265, which has been genetically modified to express NpHR. When yellow light is emitted from elongate structure 260 and falls upon neuron 265, this cell exhibits resistance to action potentials. Heat sink/mounting base 262 serves dual purposes as both a mass which conducts and diffuses heat from near the site of light generation within the device, and as a base which can be affixed firmly to skull.

The LED designed with an integrally-formed elongate structure which correlates to the dimensions of an optical fiber, for delivering light to cells with light-activated ion channels to sub-surface regions of the brain or body. The elongate structure (*e.g.*, 104, 106, 125, 210, 230, 260) can assume a smooth shape, for example a cylinder, tapering

cylinder, cone, or flat elongate rectangular shape. Such lenses may be made of a variety of clear or colored translucent materials including polycarbonate and glass. The lens is generally formed integrally and tightly fitting around the electronic elements including the diode itself, for example, by high-pressure injection molding to remove all air interposed between lens material and diode element. The lens diameter may vary depending upon the specific area that requires illumination. For example, an elongate structure of 20 mm diameter (comparable with optical fibers previously used to deliver light to deep anatomical targets), is suited to the delivery of light to the cell bodies and/or axons of small clusters of neurons. Smaller diameter lenses (for example, 10 microns or less) may be more suited to delivering light to individual cells. Use of larger diameter lenses (for example 1 mm x 1 mm square lenses or 1 mm diameter cylindrical lenses) may be useful for illuminating large swaths of targeted tissue. Smaller diameter lenses tend to be more fragile than larger diameter lenses, however, depending upon the specific material used for its composition.

The transmission element or elongate structure may have optical focusing properties, or may simply serve as a non-refractive transmission channel which physically separates the heat-generating light production portion from the heat-sensitive, optically-reactive target. The tip may be the same diameter as the base of the structure, or it may be of different dimensions.

The shape of the elongate structure may also be altered or improved after initial manufacture. For example, plastics or glass elongate structures may be molded in an initial elongate shape, then drawn out to long and thin dimensions, using methods and tools commonly used in the neuroscience laboratory for the ad-hoc creation of glass pipette electrodes for intracellular electrical recording. Using this method, glass cylinders are heated over a small area, and are then linearly stretched. At the proper length and reduced diameter, the micropipette/electrode glass is cut. This process and facilitating devices (which are commercially available) similarly serves the process of creating an elongate structure of the proper length and diameter, with the difference that a cylindrical lens with formed-in electronic elements (including the diode itself) replaces the glass cylinder used for making a microelectrode. This same process may be accomplished with plastic elongate structures, either by heating and drawing out as with glass, or by drawing out the plastic before it has cured.

The heat sink/mounting base (*e.g.*, FIG. 1A: 112, 114; FIG. 1B: 130; FIG. 2C: 262) serves dual purposes as both a mass which conducts and diffuses heat from near the site of light generation within the device, and as a base which can be affixed firmly to skull. This portion is typical at the (proximal) base of the apparatus, surrounding the active poles and diode portions of the device. This base may be sutured to tissue via holes placed in the base, and may be cemented to the skull directly, for example using a methacrylate-based compound.

FIGs. 3A and 3B depict an elongate structure for controlling light by rotational movement of the elongate structure, consistent with an embodiment of the present invention. Elongate structure 304 directs light toward the distal tip 306. The longitudinal direction 302 of elongate structure 304 shows the general direction of travel for the light. The distal tip 306 is designed to generally direct the light at an angle relative to the longitudinal direction 302. Thus, by rotating the elongate structure 304 around the distal tip (shown by arrows 310), the illumination pattern can be changed. This allows for fine-tuning of the effective delivery location for the optical stimulus. During surgical implantation, the elongate structure 304 can be rotated. At different rotational positions, light can be provided to stimulate target cells. The effectiveness of the stimulation can be assessed and the rotational position can be fixed accordingly. The assessment of the effectiveness can be tailored toward the specific goal/treatment of the implanted device.

The direction of travel for the light can be controlled using a variety of optical-based principles, such as focusing or directing light using refraction or reflection caused by differing indices of refraction. For instance, FIG. 3A shows the tip 306 being other than perpendicular to the longitudinal direction 302, such as perpendicular to direction 308. Moreover, the tip 306 can be constructed with a curve surface to further direct the light. FIG. 3B shows a section 310, which can be made from one or more materials having a different index of refraction relative to that of the remainder of elongate structure 304. Various other directing options are possible including, but not limited to, reflective material or an attached lens.

FIGs. 3C and 3D show movement of a light delivery structure within a fixation portion, consistent with an embodiment of the present invention. Fixation portion 312 allows the elongate structure 304 to rotate about the longitudinal axis. Alternatively, the elongate structure 304 can also be allowed to move along the longitudinal axis as shown by the vertical arrows in FIG. 3D.

FIG. 4 shows a light delivery structure, consistent with an embodiment of the present invention. The light delivery structure includes a lumen 404 that surrounds an opening 402. Optional outer layer 406 surrounds lumen 404. In one implementation, the lumen is made from glass or plastic, such as a pipette or micropipette. The light is directed through the lumen as discussed herein. Outer layer 406 can help direct the light along the length of lumen 404. The lumen can be filled with a material, liquid or otherwise, to provide the desired optical properties. For instance, the lumen filling material can be used to transmit the optical light by either matching the refractive index of the lumen or having an index of refraction sufficiently different from that of the lumen to provide total internal reflection within the lumen filling material.

Fig. 4 also depicts heat removal elements 408 and 410. These elements are thermally coupled with the light source, which is substantially encased within the lumen 404 and/or the outer layer 406. Heat removal element 408 is in thermal contact with the light source and dissipates heat through thermally conductive strips 410. The thermally conductive strips 410 can be connected to the fixation device or some other structure that acts as a heat sink 412. In a particular implementation, the material for lumen 404 has a high thermal resistance thereby allowing substantially all heat generated by the light source to be dissipated through the heat removal elements 408 and 410.

Further details of an example embodiment consistent with FIG. 4 include a commercially manufactured LED that is surrounded by index-matching material and contained within (or coupled to) a pipette or micropipette that serves as a light delivery element. The distal end of the pipette or micropipette is implanted at the neuronal target. The proximal end of this pipette contains the light production element. This light production element may be a standard commercially available light-emitting diode package such as the SML0805-B1K-TR (LEDtronics Inc. Torrance, CA). Suitable micropipettes may be made in accordance with standard laboratory procedures from glass tubing stock B200-156-10 and a micropipette puller machine model P1000, both available from Sutter Instrument (Novato, CA). The internal or external surface of the pipette may then be coated with a reflective substance so as to increase internal reflection. For example, "silvering" is a chemical process of coating glass with a reflective substance. In this process, the pipette may be sputtered with powdered aluminum by placing it in a vacuum chamber with electrically heated nichrome coils which sublime the aluminum.

When subsequently exposed to oxygen in an oven, a layer of durable, transparent aluminum oxide is formed.

An index-matching material may be used within the pipette and around the LED lens so as to smooth or eliminate the transition in refractive indices between the LED lens and the lumen of the pipette material by eliminating air space and approximating the refractive indices the lens materials. Index-matching liquids and materials are commercially manufactured and sold by many sources including Timbercon, Inc., Lake Oswego, OR. The index of refraction of various translucent and transparent materials, such as LED lenses, is generally available as part of a manufacturers specification or various publically available lists/databases. Another consideration is the particular wavelength(s) of light to be used as this can affect the index of refraction.

The present invention may also be used for precisely delivering light to specific target regions of the body for other phototherapy purposes. For example, some wavelengths of light are known to have bactericidal properties, while other wavelengths may induce the production of certain desired molecular products.

The various embodiments described above are provided by way of illustration only and should not be construed to limit the invention. Based on the above discussion and illustrations, those skilled in the art will readily recognize that various modifications and changes may be made to the present invention without strictly following the exemplary embodiments and applications illustrated and described herein. For instance, such changes may include the use of digital logic or microprocessors to control the emitted light. Such modifications and changes do not depart from the true spirit and scope of the present invention, which is set forth in the following claims.

What is claimed is:

1. An optical delivery device for delivering light *in vivo*, the device comprising:

a light source for producing light from electrical power;

an optical transmission element made from a material that is substantially transparent to the light from the light source, the material having an elongated shape that substantially encases the light source at a proximal end and that is for delivering the light from the light source to a distal end;

a fixation portion physically coupled to the optical transmission element for attachment to the patient; and

a heat dissipation portion having a thermally conductive path for removing heat from near the light source.

2. The device of claim 1, wherein the optical transmission element is a lumen and the material is one of glass and plastic.

3. The device of claim 1, wherein the lumen contains a substance having an index of refraction that is substantially the same as the material of the lumen.

4. The device of claim 1, wherein the optical transmission element is rigid along a direction of transmission for the light.

5. The device of claim 4, wherein the optical transmission element includes an outer layer of a second material that facilitates light traveling along the direction of transmission.

6. The device of claim 1, further including a temperature sensor for sensing a temperature near the optical transmission element and a control circuit for controlling the activation of the light source in response to the sensed temperature.

7. The device of claim 1, wherein the optical transmission element is configured to direct light along a longitudinal axis that extends from the proximal end to the distal and

wherein the optical transmission element is configured and arranged to direct light leaving the transmission element at a non-zero angle relative to the longitudinal axis.

8. The device of claim 1, wherein the fixation portion is configured and arranged to allow rotational movement, about the longitudinal axis, of the optical transmission element during implantation and to prevent the rotational movement after implantation.

9. The device of claim 1, wherein the material of optical transmission element is glass that is coated with a reflective substance.

10. The device of claim 1, further including an implantable signal source having a power supply, a control circuit for generating electrical signals that activate the light source and conductors for transmitting the electrical signals to the light source.

11. The device of claim 10, wherein the implantable signal source is designed for placement within the chest cavity in connection with the optical transmission element being implanted within the brain.

12. A method for stimulating target cells *in vivo*, the method comprising:
engineering light-activated ion channels in one or more *in vivo* target cells;
surgically implanting a device having
a light source for producing light from electrical power,
an optical transmission element made from a material that is substantially transparent to the light from the light source, the material having an elongated shape that substantially encases the light source at a proximal end and that is for delivering the light from the light source to a distal end,
a fixation portion physically coupled to the optical transmission element for attachment to the patient, and
a heat dissipation portion having a thermally conductive path for removing heat from near the light source; and
activating the light source to stimulate the target cells.

13. The method of claim 12, wherein the step of engineering further includes expressing, one or more *in vivo* target cells, light-activated ion channels that are variants of at least one of ChR2 and NpHR.

14. The method of claim 12, wherein the step of implanting further includes rotating the optical transmission element about a longitudinal axis; activating the light source to stimulate the one or more target cells; assessing the effectiveness of a rotational position as a function of stimulus results, and fixing a rotational position of the optical transmission element in response to the assessment.

15. The method of claim 12, further including the step of disabling the light source in response to a temperature sensor.

16. The method of claim 12, wherein the step of implanting is accomplished using stereotactic insertion of the optical transmission element.

17. The method of claim 12, wherein the one or more *in vivo* target cells are neurons.