

LIGHTING A PATH TO PRECISION MEDICINE

Regulatory and Policy Implications of Optogenetic Technology

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EXECUTIVE SUMMARY

Optogenetics is a bioengineering technology that allows for precisely timed control of brain cells using light. The technology involves adapting genes of light-responsive proteins found in microbial species such as algae to uses in animal and human tissues. Recently, the U.S. Food and Drug Administration has authorized clinical trials for the first-ever human use of optogenetic gene therapy, for treatment of a form of blindness. New biotechnology startups have sprung up with plans to bring optogenetics to the U.S. health care market. Wide-ranging clinical applications, from unique therapies for neurological and psychiatric disorders to new solutions for cardiac problems, make this technology an innovative player in the next generation of precision medicine.

This paper begins with a review of the latest scientific developments in optogenetics, followed by a discussion of the safety and effectiveness issues in clinical optogenetic applications and the complexities of the existing FDA regulatory pathways for approval of optogenetic therapy. The paper concludes by addressing larger social and policy questions surrounding the future use of optogenetics for human-enhancement purposes. Optogenetics is a potentially revolutionary medical technology and the current regulatory and policy landscape may determine its ultimate reach.

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INTRODUCTION

In 1979, Francis Crick, one of the discoverers of the structure of the DNA molecule, foresaw the need for “a method by which all neurons of just one type could be inactivated, leaving the others more or less unaltered,” to fine-tune our understanding of brain function.¹ Nearly 30 years later, Crick’s vision was brought to life with the introduction of optogenetics to the field of modern-day neuroscience. Optogenetics has been defined as “a method that uses light to control cells in living tissue, typically neurons, which have been modified to express light-sensitive ion channels and pumps.”² In 2010, the journal *Nature* declared optogenetics the “method of the year,” while *Science* named it the “breakthrough of the decade.”³ This paper provides a systematic description of optogenetic technology with a focus on clinical applications, and discusses the regulatory and policy hurdles and opportunities for bringing optogenetic therapy to the U.S. health care market.

What is Optogenetics?

Optogenetics is a technology that allows chosen cells to be controlled using light. Light-activated proteins, called opsins, occur naturally in a range of prokaryotic species such as archaea, bacteria, fungi, and algae, in which they support many functions including phototaxis, energy storage, and various signaling mechanisms.⁴ Such a protein sits inside of a cell’s membrane and upon interaction with a photon of light, the protein undergoes a structural change which. Depending on the opsin type, that change either opens a channel in the protein to allow ions (i.e., charged atoms) to flow in or out of the cell or initiates a biochemical-signaling cascade inside of the cell. One example of opsin function is to control the organism’s movement to direct phototaxis toward environments with optimal light intensities for photosynthesis.⁵ These opsins were first discovered in the 1970s, starting with bacteriorhodopsin, found in the species *Halobacterium salinarum*, which pumps protons out of cells in response to green light. That was followed by the discovery in the same species of halorhodopsin, which pumps chloride

into cells in response to yellow light.⁶ More recently, the channelrhodopsin-2 (ChR2) was discovered in the green algae *Chlamydomonas reinhardtii*. ChR2 is an ion channel that opens to allow cations (i.e., positively charged atoms such as H⁺ and Na⁺) to flow into a cell upon exposure to blue light.⁷ The discovery of ChR2 immediately implied the potential for use in mammalian neurons since neurons naturally depolarize (i.e., “turn on”) by letting positively charged ions through their membranes — implying that ChR2 could be expressed in neurons to activate them at will with light.

With the precise goal in mind of turning neurons on with light, in 2005, Boyden and colleagues expressed ChR2 in rat neurons *in vitro* by transfecting the cells with a lentiviral vector packaged with the cloned ChR2 gene.⁸ Following successful transfection, the authors of the study were able to activate neurons (i.e., cause the cell to “spike”) with millisecond precision for up to 30 Hz of blue light stimulation.⁹ Furthermore, ChR2 expression remained stable for weeks, and cell health did not appear to be affected by the insertion of these exogenous channels into cell membranes.¹⁰ The next breakthrough in optogenetics occurred in 2007 with the successful use of ChR2 to precisely control whisker movement *in vivo* in rodents by shining light on specific regions of the motor cortex.¹¹ Importantly, in order to achieve such a targeted effect, expression of ChR2 was restricted to specific cells, excitatory cells, in the motor cortex that initiate movement by adding the alpha calcium/calmodulin-dependent kinase II (CaMKII α) promoter to the virus, which only excitatory cells are able to express.¹² Many different promoters can be used when engineering viral vectors for opsin gene delivery, thereby ensuring that opsins are expressed only in cell types of interest. When a large region of the brain is exposed to blue light, only those cells that express the opsin will be activated.

Optogenetics is therefore characterized by three core features: microbial opsins adapted from organisms such as algae and archaea, a method for targeting opsin gene expression to specific cell types, and a method for delivering timed light to

specific brain regions or other organs.¹³ While manipulating the activity of neurons is as old as neuroscience itself — for example, by using electrical stimulation or pharmacology — optogenetics offers control that is more precise than electrical stimulation since opsins can be genetically targeted to be expressed in *specific* cells, and control that is *faster* than pharmacology given the slow effect of drug action. Optogenetics offers an unprecedented ability to control specific cell types with precise timing, opening the door to real-time therapeutic control of complex physiological functions.

The Optogenetic Toolbox

Following promising studies with blue-light-responsive ChR2 for activating neurons, an entire “toolbox” of engineered opsins has been rapidly developing, allowing for a rich variety of catered physiological effects to be realized.¹⁴ Halorhodopsin derived from the species *Halobacterium natronomonas pharaonic* (NpHR) has the opposite effect of ChR2, silencing cells instead of activating them, by pumping Cl⁻ into the cell.¹⁵ By expressing both ChR2 and NpHR in the same cells, cells can be turned on with blue light and turned off with yellow light, with great precision. A synthetic opsin, ChETA, was engineered to have faster kinetics than the natural ChR2, thereby allowing cells to be driven as fast as 200 Hz with blue light stimulation.¹⁶ On the other hand, another type of engineered opsin class, called the Step Function Opsins (SFOs), have very slow kinetics which allow for a subthreshold activation of cells, without dictating specific firing patterns, producing a more “natural” way to turn cells on.¹⁷ OptoXRs have been engineered to act as G-protein coupled receptors, which are activated by exposure to green light. Instead of allowing ions to flow in and out of the cell, they initiate a biochemical-signaling cascade inside of the cell that can, for example, result in the upregulation of specific genes inside the nucleus.¹⁸

Armed with this rich toolbox of optogenetic technology, investigators have explored many clinical applications of optogenetics.

PART I: CLINICAL APPLICATIONS

To date, the most promising clinical applications of optogenetic technology have been for the treatment of neurological and psychiatric diseases and conditions. The complexity of the nervous system and the myriad genetic, biological, and environmental factors that contribute to dysfunction make neurological and psychiatric diseases ripe for disruption in medical treatment. The following section discusses several neurological/psychiatric disorders that have been investigated using optogenetics and more recent medical applications outside of the nervous system.

A. Epilepsy

Epilepsy is a category of neurological disorders marked by recurrent seizures caused by abnormal, over-excitability electrical brain activity with no apparent underlying cause.¹⁹ A major concern is drug resistance in many forms of epilepsy, necessitating a new therapeutic approach.²⁰ In an *in vivo* rodent model of neocortical epilepsy, Wykes and colleagues transfected neocortical neurons with a lentivirus containing halorhodopsin, which silences neurons in response to yellow light. By delivering yellow light repeatedly, the researchers were able to dampen the overly active cells and attenuate seizures.²¹ Instead of arbitrarily delivering yellow light to silence cells expressing halorhodopsins, Paz and colleagues recorded electrical activity from the brains of rodents and used an algorithm to detect seizures, which triggered yellow light to halt seizures immediately after onset.²² Within the next decade, researchers hope to be able to predict seizures *before* onset and to use optogenetics to prevent them from ever taking place.²³

B. Drug Addiction

In a rodent model of drug addiction, rats will continue to self-administer cocaine even when the drug-seeking behavior leads to painful foot shocks. Chen and colleagues showed that after

prolonged drug-seeking behavior, rats have decreased activity in a specific cell type in a part of the brain called the prefrontal cortex.²⁴ The researchers delivered viral vectors with a certain promoter (i.e., DNA region that activates a gene) to specifically express ChR2 in these affected cells. Applying blue light stimulation to this part of the brain activated these cells and reduced drug-seeking behavior in the rats.²⁵ In a similar vein, Whitten and colleagues identified a different brain region, the nucleus accumbens, where a specific cell type is known to be overactive in drug addiction. After applying yellow light to inhibit these cells, which were transfected to express halorhodopsin, drug-seeking behavior in mice was reduced.²⁶

C. Alzheimer's Disease

Alzheimer's disease is a progressive neurodegenerative disease characterized by dementia and short-term memory loss that ultimately lead to speech and motor function disturbance and eventually death.²⁷ There is no currently available cure for Alzheimer's, treatment options are limited, and the underlying cause is poorly understood.²⁸

Neuronal death in Alzheimer's is associated with specific molecular pathology, including the presence of amyloid beta (A β) plaques and neurofibrillary tangles.²⁹ A β plaques are composed of amyloid-beta peptide deposits that aggregate together outside of cells and tangles are made up of microtubule-associated tau proteins that accumulate inside cells.³⁰ Although the relationship between such molecular pathology and physiological function in Alzheimer's is obscure, studies have shown that increases in certain types of neural activity are correlated with increases in A β plaques.³¹ A type of brain wave activity called gamma rhythm is disrupted in animal models of Alzheimer's disease and in human patients with Alzheimer's.³² A study by Iaccarino and colleagues sought to test this relationship by expressing ChR2 in a specific cell type, interneurons, in a brain region called the hippocampus using a mouse model of Alzheimer's disease.³³ Interneurons are known to play a causal role in the gamma rhythm, and by activating these cells using 40 Hz blue light stimula-

tion, the researchers were able to induce gamma rhythms and consequently reduce both A β plaques and tau tangles.³⁴ Thus, optogenetics allowed for a causal test of a pathophysiological relationship in Alzheimer's disease and could offer new therapeutic targets.

D. Parkinson's Disease

Parkinson's disease is a neurodegenerative disease affecting the motor system caused by degeneration in a specific cell type, dopamine neurons, in a brain region known as the basal ganglia. In a rodent model of Parkinson's, Kravitz and colleagues treated the disease symptoms by using optogenetics to stimulate a subtype of dopamine neurons in the basal ganglia.³⁵ However, given that Parkinson's is marked by progressive loss of dopamine neurons, optogenetically stimulating existing neurons is a time-limited therapeutic solution. In a study by Tonnsen and colleagues, grafted stem-cell-derived dopamine neurons were transfected to express ChR2 and injected into the basal ganglia. These cells were shown to be integrated functionally into the basal ganglia network by applying light stimulation.³⁶ Therefore, optogenetics could potentially be combined with stem cell therapy to restore lost function in Parkinson's patients.

E. Mood Disorders

Every year, about 10 percent of the U.S. population experiences some type of mood disorder, including anxiety and depression.³⁷ As with virtually all psychiatric conditions, traditional pharmacological treatments are available but limited in effectiveness, with some individuals showing complete resistance to drug treatment.³⁸ A brain structure called the amygdala plays a crucial role in mood regulation and anxiety.³⁹ Specifically, a projection from one part of the amygdala (basolateral amygdala) to another part of the amygdala (central nucleus) is believed to be responsible for anxiety-related behavior.⁴⁰ By expressing ChR2 in the basolateral amygdala and stimulating only the projections to the central nucleus (by shining light only on that projection), Tye and colleagues re-

duced anxiety behavior in mice.⁴¹ Optogenetics has been applied to target depression as well. Warden and colleagues demonstrated an antidepressant-like response in mice to illumination of specific types of neurons that play a role in depression, medial prefrontal cortical neurons, which expressed ChR2.⁴² Unlike electroconvulsive therapy (ECT), which is given in the United States in severe cases of pharmacoresistant depression but stimulates large parts of the brain indiscriminately, optogenetics offers a much more targeted stimulation approach.⁴³

F. Spinal Cord Injuries

Spinal cord injury (SCI) typically occurs following physical trauma to the spinal cord and, depending on the severity of the injury, can show poor prognosis given the limited regenerative capacity of the central nervous system.⁴⁴ One major obstacle is that following the injury, damaged motor neurons remain dormant (i.e., inactive) therefore preventing potential regeneration.⁴⁵ In a study performed by Alilain and colleagues, the authors introduced the ChR2 gene into the gray matter of the spinal cord after a SCI was induced in rats.⁴⁶ Activation of ChR2 with blue light promoted recovery of muscle activity and restoration of respiratory activity.⁴⁷ In a study by Bryson and colleagues, motor neurons were generated from stem cells that express the ChR2 gene and were engrafted into partially denervated branches of the sciatic nerves of mice.⁴⁸ These neurons reinnervated muscles and restored muscle function following optogenetic stimulation.⁴⁹ Optogenetic therapy may therefore be used to at least partially restore lost motor function in patients with spinal cord injury.

G. Cardiac Applications and Beyond

Although the majority of optogenetic studies have focused on neurological disorders, partially due to the technology's emergence out of the neuroscience community, recent applications have extended to include more diverse applications of optogenetic techniques. Cardiac optogenetics is a

growing field of study that utilizes opsins expressed in heart tissue to control cardiac pacing, which has the potential for use as a therapy for cardiac arrhythmia.⁵⁰ Optogenetics allows control of specific cardiac cell types, while conventional electrotherapy for arrhythmia electrically stimulates tissue indiscriminately and can cause severe pain from activation of surrounding skeletal muscle.⁵¹ Opsin delivery to cardiac tissue has been reported *in vivo* in animal models and *in vitro* in human adult heart tissue.⁵²

In addition to real-time control of excitable cells such as neurons and cardiac cells, optogenetics has been creatively adapted for control of gene expression and gene editing. A special form of CRISPR-Cas9 technology, named the CRISPR/Cas9 effector (LACE) system, has been engineered to activate upon exposure to blue light.⁵³ LACE allows for optogenetic control of the expression of any desired gene with a known regulatory element.⁵⁴ Similarly, a different form of CRISPR-Cas9 technology has been engineered to reversibly switch on and off targeted gene editing (rather than simply gene expression) with exposure to blue light.⁵⁵

PART II: SAFETY, FEASIBILITY, & LIMITATIONS

The clinically relevant optogenetic studies discussed thus far have all been performed in animal models. Although opsins have yet to be delivered into a living human brain, the feasibility of doing so has been partially demonstrated by expressing ChR2 *in vitro* in brain slices obtained from adult humans who had brain tissue resected due to intractable epilepsy.⁵⁶ In this preparation, human neurons were successfully controlled with light in the same way as in animal studies.⁵⁷ Although optogenetic use in human patients would constitute a highly novel treatment option with little current guarantee of safety and effectiveness, this should not be viewed as an ultimate barrier.

Deep brain stimulation (DBS) is one of the only currently approved FDA treatments that is intended to modify brain circuit activity and involves implanting electrodes, which stimulate brain regions at high frequencies.⁵⁸ More than 100,000 patients receive DBS treatment worldwide for Parkinson's disease, essential tremor, and dystonia, among other neurological disorders, despite a poorly understood mechanism of action and a host of serious side effects.⁵⁹ Likewise, the FDA has recently cleared another less invasive brain stimulation treatment, transcranial magnetic stimulation (TMS), which delivers pulses of magnetic stimulation to specific brain regions from outside of the skull.⁶⁰ TMS is used for the treatment of depression, yet its mechanistic underpinnings are also poorly understood.⁶¹ Optogenetics promises an innovative therapeutic solution with greater specificity and precision in comparison to the more traditional and crude DBS and TMS methods. However, for the potential of optogenetic therapy to be fully realized, some important safety issues must be addressed, namely issues pertaining to the expression of foreign opsin genes in human tissue, the use of viral vectors to deliver these genes, and mechanisms for delivering light stimulation to activate the opsins. These three issues are discussed in detail below.

A. Opsin Proteins

Opsin genes are genes cloned from foreign unicellular species and expressed in mammalian cells by being embedded as proteins within the cellular membrane. It is no surprise that integrating foreign molecules into cellular membranes has potential consequences for cellular health. It has been shown that there is a threshold level of safe opsin expression in neurons and that overexpression, or putting too many opsin channels into the membrane, can result in neuronal swelling.⁶² In addition, ChR2 expression has been shown to cause changes to the electrical properties of neurons, such as an increase in membrane capacitance.⁶³ These findings point to disturbances in cellular function caused by opsin expression. On the other hand, some findings suggest that ChR2 can be well-tolerated in animal brains *in vivo* for

up to one year of follow-up.⁶⁴ Nevertheless, optogenetic researchers recommend that experiments using optogenetics should include histological and electrophysiological validation of cellular health to detect potential toxic effects of opsins, which can allow for optimization of safe expression levels.⁶⁵

B. Viral Vectors

Optogenetic technology requires delivering foreign opsin genes to mammalian cells which rely on the cell's endogenous machinery to translate these genes into functional proteins embedded into cell membranes. The most common way of achieving opsin expression is by transfecting cells with viral vectors that carry the opsin gene. Naturally occurring viral genomes are edited to remove pathogenic functions and replaced with the desired genes — in this case opsin genes.⁶⁶ Furthermore, in order to restrict opsin expression to specific cell types, these viral vectors are engineered to include a promoter genetic sequence (placed in front of the opsin gene) which ensures that only the cell type of interest has the right transcription factor to turn on gene expression.⁶⁷ For example, the CaMKII α promoter is specific to excitatory neurons in specific brain regions (i.e., cortex and hippocampus), while fSST is specific to inhibitory neurons.⁶⁸ These engineered viral vectors retain their invasiveness and can infect host cells to inject their genetic material into the cell's cytoplasm or in some cases, depending on the virus used, integrate into the host's genome.⁶⁹ Unlike traditional pharmacological products with half-lives, genetic vectors may expose a patient to gene products indefinitely, which comes along with various safety concerns such as potential oncogenesis from random insertion of the genes contained in the virus or an adaptive immune response to the virus or the opsin gene itself.⁷⁰ In light of these risks, the two most clinically relevant viral vector types, the adeno-associated virus (AAV) and lentivirus, are discussed below.

I. Adeno-Associated Viruses

In general, AAV class viral vectors are considered the safest for human applications given that gene

expression can last for years with low potential for immunogenicity (i.e., immune response), pathogenesis, and mutagenesis.⁷¹ Additionally, AAV vectors are designed to lack the ability to integrate genes into the host genome and have therefore been rated as biosafety level (BSL) 1 or 2 agents.⁷² Although integration into the host genome may be desired for some applications, since neurons generally do not divide, they are able to express opsins for long periods of time, without the need for ongoing gene expression.⁷³ Given the added safety risks associated with integrating genes into the host genome, AAVs can provide a safe and effective method for delivering opsins to nondividing cells such as neurons and cardiac cells.

There are dozens of ongoing clinical trials in the United States assessing safety and effectiveness of AAV vectors for gene therapy. In 2005, a clinical trial using AAV gene therapy in patients with advanced Parkinson's disease demonstrated that therapy was well tolerated, with no adverse effects attributable to gene therapy.⁷⁴ More recently, a phase I/II study using AAV gene therapy for patients with Leber congenital amaurosis (an eye disorder) to replace a mutated gene showed no incidents of adverse events with either a low or high dose of AAV therapy.⁷⁵

2. Lentiviruses

Lentiviral vectors support high levels of gene expression and are generally nonpathogenic and with low immunogenicity potential. Although originally AAV vectors were much safer than lentiviral vectors, third-generation lentiviral vectors are considered safe for gene therapy applications.⁷⁶ There are at least two-dozen ongoing clinical trials in the United States for gene therapy using lentiviral vectors for a variety of diseases.⁷⁷ A recent phase I/II clinical trial using lentiviral vector genetic therapy in patients with Parkinson's disease supports the safety of lentivirus for gene therapy.⁷⁸ However, unlike AAVs, lentiviral vectors integrate genes into the host genome.⁷⁹ Therefore, in most cases lentiviral vectors may be less desirable for optogenetic therapy targeting nondividing cells. In any case, both AAV and len-

tivirus methods for optogenetics would require biodistribution testing to determine the expression of the vector and gene products in both on- and off-target cells and to assess the optimal dose level.⁸⁰

C. Light

Once opsins are expressed in cells of interest, they need to be activated by applying light of the right wavelength (e.g., blue light for ChR2 and yellow light for halorhodopsins). In animal studies, this is achieved by implanting guide cannulas in the brain region of interest (where opsins are expressed) and inserting an optical fiber that uses either laser diodes or LEDs through the cannulas for targeted light delivery.⁸¹ In order to allow for both optogenetic stimulation and simultaneous recording of brain activity, an optical fiber cable is attached to a recording electrode, forming an "optrode."⁸² These approaches work well in chronic animal studies but are highly invasive, requiring surgery and implantation of large cannulas that damage brain tissue along their tracts. Moving towards a less invasive approach, new types of electrodes have been developed with embedded micro-LEDs one thousand times smaller than conventional LEDs, which can allow deep brain penetration with less tissue damage.⁸³

However, all of these techniques require cables to be connected to hardware that drives light delivery and electrical recording. A promising approach involves a wireless optrode that contains a radio frequency harvesting unit that receives signals from a transmitter, allowing for this device to be implanted and controlled wirelessly from outside of the brain.⁸⁴ Another wireless approach that doesn't involve radio frequencies is using special nanoparticles called Upconversion Nanoparticles (UCNPs).⁸⁵ Since currently available opsins can only respond to light wavelengths within the visible light range, but not to longer wavelengths that can penetrate deeper into tissue, the light needs to be delivered close to the target brain region.⁸⁶ UCNPs absorb near-infrared (NIR) light, which can penetrate deep tissue, and in turn emit wavelength-specific visible light (e.g., blue light).⁸⁷ In an experiment by Chen and colleagues, the re-

searchers injected UCNPs into a localized brain region and delivered NIR light from outside the skull to optogenetically control cells expressing ChR2 in deep tissue.⁸⁸ These new wireless approaches can offer more clinically suitable options for light delivery in optogenetic therapy interventions in human patients.

D. Limitations

A major current limitation of optogenetic approaches is that the vast majority of optogenetic studies have been “open loop,” meaning that light is delivered in an arbitrary manner rather than in response to meaningful brain activity. Closed-loop optogenetics requires recording neural activity or behavior to make real-time decisions about when and how to deliver light stimulation.⁸⁹ Paz and colleagues used real-time monitoring of brain activity in rats with an epilepsy-like condition and upon detection of seizure onset; optogenetic inhibition of specific cells was triggered using yellow light, which successfully interrupted seizures.⁹⁰ This study demonstrates the feasibility of creating a truly closed-loop feedback system for optogenetic therapy.

A related issue is delivering physiologically relevant optogenetic stimulation patterns. Currently, light is delivered at a chosen frequency (e.g., 40 Hz), which simultaneously activates all cells expressing opsins that respond to the delivered light. However, such a strategy is a crude and artificial way of activating neurons, since natural neural activity is characterized by complex and intricate firing patterns within ever-changing neural network ensembles. This means that current optogenetic light delivery protocols are likely sending a “message” to the brain in a “language” that the brain cannot properly interpret. The issue is twofold: first, there are limited options available for honing in light delivery to individual cells and second, even if such single-cell precision was possible, physiologically relevant firing patterns are poorly understood. Therefore, future optogenetic experiments may focus on methods and protocols for delivering physiologically meaningful patterns of light stimulation to a network of cells.⁹¹

PART III: COMMERCIAL APPLICATIONS

Despite existing concerns and limitations, optogenetics has recently made its way from bench to bedside. A company called RetroSense Therapeutics (recently bought out by Allergan Inc.) was granted Orphan Drug Designation by the FDA for an optogenetic therapy for Retinitis pigmentosa, a form of blindness.⁹²

Orphan Drug Designation is granted to drug/biologics developers for diseases that affect less than 200,000 people in the United States.⁹³ In Retinitis pigmentosa, the photoreceptors in the retina, rods and cones, which contain the only natural opsins in the human body, are missing and therefore cannot transduce visible light into an electrical signal that can travel through the brain, making its way to the visual cortex where visual information can be processed.⁹⁴ In the RetroSense clinical trial, which commenced in 2016, the first-ever optogenetic therapy in the world was delivered to patients with Retinitis pigmentosa with the goal of delivering algae opsins (i.e., ChR2) to another cell type in the retina, ganglion cells, which are downstream of the missing photoreceptors.⁹⁵ Phase I of this trial did not raise any safety issues thus far and reported a rudimentary level of vision restoration in these patients.⁹⁶ This clinical trial was not only the first time optogenetic treatment was applied in humans, but also marked the first time that nonhuman DNA was delivered as gene therapy in a human.⁹⁷ Similarly, in 2017, the FDA granted Orphan Drug Designation to another company called GenSight for optogenetic treatment of Retinitis pigmentosa that will utilize an external wearable device to more precisely stimulate the opsins by amplifying the light signal.⁹⁸

Circuit Therapeutics is working on applying optogenetics for pain therapy. Although still in early stages, the idea is to deliver opsins to specific nerve endings directly under the skin and, since light can easily penetrate skin, to apply light

through a flexible adhesive LED patch to temporarily silence the pain-causing neural activity.⁹⁹ Unlike other pain interventions that inhibit activity of all cell types, targeting opsin expression to specific cells and applying light temporarily would allow a patient to retain nonpainful sensation.

These emerging innovations in optogenetic therapy, coupled with unprecedented recent FDA approvals for other gene therapies, open the door for commercial potential in this space. In the past several years, the FDA has authorized over 1000 Investigational New Drug (IND) applications for human gene-therapy clinical trials.¹⁰⁰ However, none of these trials led to commercial distribution through a Biological License Application (BLA) approval until 2017, when Kymriah became the first approved gene therapy available in the United States, used to treat a form of leukemia.¹⁰¹ Kymriah is an *ex vivo* treatment in which the patient's cells (T-cells) are extracted, genetically modified, and then re-introduced into the body.¹⁰² Most recently, in December of 2017, a company called Spark Therapeutics received distribution approval for the first *in vivo* gene therapy, Luxturna, to treat inherited retinal disease by delivering a correct copy of a retinal gene through an AAV viral vector.¹⁰³

In contrast to the currently approved gene therapies, optogenetic therapies are likely to undergo a more complicated FDA approval process given that they combine *in vivo* viral vector delivery with a gene foreign to the human body, and simultaneously require medical device approvals for light delivery. The next sections explore various FDA regulatory pathways that are relevant for bringing optogenetic therapies to market.

PART IV: FDA REGULATIONS

The FDA regulates three main classes of medical products: drugs, biological products, and medical devices.¹⁰⁴ Optogenetic therapy can be broken down into two main components: 1) viral delivery of an opsin gene, which constitutes gene therapy

and falls under a biological product and 2) mechanisms for light delivery, which will generally fall under medical devices. Biological product regulations are discussed first, followed by a discussion of medical device regulations.

While the Food and Drugs Act (FD&C Act) deals with traditional small-molecule drugs and medical devices, biological products are dealt with under the Public Health Service Act (PHSA). The PHSA defines a biological product as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product ... or analogous product ... applicable to the prevention, treatment, or cure of a disease or condition of human beings."¹⁰⁵ Biological products under the PHSA include gene therapy products, which are under the regulatory oversight of the Office of Tissues and Advanced Therapies (OTAT) within FDA's Center for Biologics Evaluation and Research (CBER).¹⁰⁶ The first gene-therapy-specific guidance document released by the FDA in 1998 defined gene therapy as follows:

Gene therapy is a medical intervention based on modification of the genetic material of living cells. Cells may be modified *ex vivo* for subsequent administration to humans, or may be altered *in vivo* by gene therapy given directly to the subject. When the genetic manipulation is performed *ex vivo* on cells which are then administered to the patient, this is also a form of somatic cell therapy. The genetic manipulation may be intended to have a therapeutic or prophylactic effect, or may provide a way of marking cells for later identification. Recombinant DNA materials used to transfer genetic material for such therapy are considered components of gene therapy and as such are subject to regulatory oversight.¹⁰⁷

Following the release of this first gene therapy guidance, the initial enthusiasm for gene therapy waned following the 1999 death of teenager Jesse Gelsinger, who participated in a phase I gene therapy clinical trial for ornithine transcarbamylase (OTC) deficiency.¹⁰⁸ His death was caused by an immune response to the viral vector used for gene delivery.¹⁰⁹ In response, the FDA created the Gene Therapy Clinical Trials Monitoring Plan to

strengthen oversight over gene therapy clinical trials and improve reporting of adverse events.¹¹⁰ This unfortunate incident set back gene therapy development for many years.¹¹¹ The recent market approval of Kymriah therefore marks a monumental turning point for the future of human gene therapy.

The regulatory pathway for gene therapy follows the general pathway for all biological products, starting with an Investigational New Drug (IND) application granting pre-approval for clinical trials, followed by FDA review of a Biological License Application (BLA) and finally case-specific, ongoing post-approval and postmarket monitoring of patient safety.¹¹² Before submitting an IND to the FDA, a gene therapy developer begins by submitting a proposed clinical trial protocol to the National Institutes of Health (NIH) Recombinant DNA Advisory Committee (RAC) as well as their local Institutional Review Board (IRB) and Institutional Biosafety Committee (IBC).¹¹³ While the IRB and IBC are mandated to only consider safety issues, the role of the RAC has expanded over the years to include social and ethical considerations regarding the proposed therapy in addition to safety issues.¹¹⁴ The RAC sends its review to the IBC, IRB, and FDA, and decides whether public review is necessary.¹¹⁵ While technically RAC provides nonbinding recommendations, the IND application is usually updated in accordance with these recommendations because the FDA takes the RAC recommendations into account when reviewing IND submissions.¹¹⁶

Once the revised IND makes its way to the FDA, the FDA balances potential benefits and risks to clinical trial participants when reviewing the submission.¹¹⁷ In an IND application, the sponsor must describe the clinical protocol including phase I, II, and/or III studies, along with planned starting dose, dose escalation, route of administration, dosing schedules, definition of patient population, and safety monitoring plans.¹¹⁸ The application will also include details on product manufacturing, safety and quality testing, purity and potency, as well as preclinical, pharmacological, and toxicological testing.¹¹⁹ In requirements specific to gene therapy products, the IND must ad-

dress additional issues (discussed in more detail below), including potential adverse immune responses to the *ex vivo* cells or the *in vivo* vector and to the gene product itself.¹²⁰ The FDA can approve the IND in its submitted state or it can put the clinical trial on hold while requesting more data from the sponsor to address lingering concerns.¹²¹

Since the release of its first guidance document for gene therapy two decades ago, the FDA has released several additional guidance documents focusing on a variety of unique safety concerns for gene therapy products.¹²² Special considerations for gene therapy include the potential for prolonged or permanent effects of the gene product after a single administration, immunogenicity, and invasive procedures to administer the product.¹²³ FDA elaborates on these considerations at every stage of the regulatory lifecycle, from pre-clinical studies to clinical trials and long-term monitoring after market approval.

A. Preclinical Studies

Preclinical studies are conducted in animals with the main objectives of identification of a biologically effective dose range for the gene therapy product as well as a dosing regimen, assessment of safety of the chosen route of administration (e.g., viral vector) and biodistribution of the product to ensure it reaches the target site but not off-target sites, and identification of potential toxicity and other safety issues such as immune responses.¹²⁴

With regard to viral vectors, the FDA recommends that preclinical studies for gene therapy examine the potential for unintended insertion of the delivered gene into the host genome as well as mutagenesis, altered expression of host genes, and oncogenicity.¹²⁵ Furthermore, potential for germline transmission and creation of replication-competent viruses should also be investigated.¹²⁶ Even for AAVs, which, as discussed above, lack the capacity for integration into the host DNA, the FDA nevertheless recommends testing for this unlikely possibility. To monitor systemic immune reactions, the FDA suggests immunoassays to measure cellular and humoral immune responses

to the vector and to the final protein product (i.e., the opsin in the case of optogenetics).¹²⁷ In addition, it is recommended that preclinical studies include a group of immunodeficient animals (i.e., animals engineered to lack an immune system) in order to assess the long-term safety of gene therapy products.¹²⁸

B. Clinical Trials

The objective of early-phase clinical trials (phases I/II) is an evaluation of safety, including correlating adverse reactions to the therapeutic dose level.¹²⁹ Since effectiveness of treatment is not a priority for early-phase trials, the FDA considers gene therapy to have a high-risk profile that does not warrant the use of a control group of healthy human participants.¹³⁰ However, the FDA still suggests that an early assessment of potential clinical benefit in the patient participants is important for gene therapy products given their high risk and novelty.¹³¹ The safety concerns that are described in the recommendations for preclinical studies apply equally to clinical trials in humans, including biodistribution, immune responses, and toxicity.¹³² Importantly, the FDA suggests testing for evidence of replication-competent retrovirus (RCR) in patients through measurement of RCR-specific antibodies and analysis of patient peripheral blood mononuclear cells to look for RCR-specific DNA sequences.¹³³

C. Long Term Follow-Up

After a clinical trial is completed, even if a gene therapy product is approved for the market, long-term follow-up and continuous submissions to the FDA may be required. The FDA recommends different long-term follow up time courses for different viral vectors. A 15-year follow-up is recommended for lentiviral vectors since they integrate into the host DNA, while only five years is recommended for AAVs, which have a low propensity for integration.¹³⁴ The 15-year protocol involves designing a plan for patients to have scheduled visits with health care professionals for the first five years that include physical examinations and laboratory testing.¹³⁵ For the following

years, participants are to be contacted once per year and asked a series of health-related questions over the phone.¹³⁶

D. Light Delivery

1. Nanoparticles

As discussed above, one method for achieving wireless optogenetic light stimulation is by using UCNPs, which absorb near-infrared (NIR) light and in response emit visible light. UCNPs are nanoparticles that are regulated by the FDA as “drug products.”¹³⁷ An FDA guidance document on nanoparticle drug products explains that materials in the nano size range (1 nm to 100 nm) can exhibit unusual physical, chemical, and biological properties, which call for special safety considerations.¹³⁸ The FDA recommends describing chemical composition, particle distribution, and stability of the nanoparticles, including pharmacokinetic-pharmacodynamic properties.¹³⁹ As with viral vectors and gene products, nanoparticles need to be assessed for their propensity to initiate an immune response, since engineered nanoparticle drug products such as UCNPs are foreign to the human body.¹⁴⁰

2. Medical Devices

The more traditional method for delivering light to brain tissue in an optogenetic protocol is by implanting a light source directly into the brain. Newer methods allow for implanting the light source and activating it wirelessly from outside of the skull. An implant for the purpose of optogenetic light delivery would fall under the FDA regulations for medical devices. A medical device is defined in the FD&C Act as:

An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article ... intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals ... which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon

being metabolized for the achievement of its primary intended purposes.¹⁴¹

Medical devices are categorized into three classes according to their safety risk level. Class I devices have the lowest risk levels and only require device manufacturers to meet certain general control standards. Class II devices are moderate-risk devices and require special controls in addition to general controls, and Class III devices are of the highest risk and require a premarket approval application (PMA) that generally includes clinical investigations.¹⁴² Implantable devices requiring surgery are always considered Class III devices, and therefore it is highly probable that implanted optogenetic light-delivery devices will also fall into the highest risk category, requiring a PMA.¹⁴³

3. Wireless Medical Devices

There are additional regulatory considerations for implanted light-delivery devices that are controlled wirelessly to optogenetically activate cells. Both the FDA and the Federal Communications Commission, which oversees the use of the public Radio Frequency (RF) spectrum within which wireless medical devices operate, regulate wireless medical devices.¹⁴⁴ The FDA guidance dealing with RF wireless medical devices suggests that manufacturers take into account the integrity of data transmitted wirelessly and cybersecurity.¹⁴⁵ In addition, manufacturers should consider the choice of RF in light of any potential electromagnetic compatibility (EMC) issues causing interference between wireless technologies using the same frequency.¹⁴⁶ RF interference is potentially a serious issue for optogenetic control of brain circuits if the interference either disrupts or activates the light-emitting device implanted in a person's brain.

PART V: EXPEDITED REGULATORY PROGRAMS

Optogenetic therapy implicates a complex web of regulatory considerations, which could impede a

path to market for this innovative class of treatments that hold potential for mitigating intractable diseases. However, the FD&C Act allows for several expedited pathways designed specifically to get innovative therapies to market more rapidly, and optogenetic therapy may be an appropriate candidate for these programs.¹⁴⁷ An optogenetic therapy may benefit from fast track designation, accelerated approval, breakthrough therapy designation, or regenerative medicine advanced therapy designation (RMAT).¹⁴⁸ These designations make a new product potentially eligible for either priority review or accelerated approval from the FDA.¹⁴⁹ An optogenetic therapy developer would need to request FDA consideration for one of these designations within the standard IND application.

A. Fast Track Designation

To be eligible for fast track designation, an investigational new drug or biological product that is intended to treat a serious condition must demonstrate through nonclinical or clinical data the potential to address an unmet medical need.¹⁵⁰ Advantages of this designation include an expedited review of the product and increased access to the FDA, as well as a rolling review of the BLA, which is needed for market approval.¹⁵¹ Optogenetic therapies have a wide range of potential applications in diseases with “unmet medical needs” that don't respond to traditional drug treatment, which suggests that they may succeed in receiving fast track designation.

B. Breakthrough Therapy Designation

While fast track designation requires only that nonclinical or clinical data demonstrate the *potential* to address an unmet medical need, breakthrough therapy designation requires a higher threshold — preliminary clinical evidence that the product may demonstrate a *substantial improvement* over existing therapies.¹⁵² Breakthrough therapy designation affords the same benefits as fast track designation, in addition to ongoing engagement with the FDA and guidance on the

product-development process throughout its lifecycle.¹⁵³ Depending on the specific use of a given optogenetic therapy and the available clinical evidence, it can benefit from breakthrough therapy designation for showing improvement over existing treatments.

C. Regenerative Medicine Advanced Therapy Designation

The most recently added expedited program is the RMAT designation.¹⁵⁴ In 2016, the FD&C Act was amended, creating the RMAT designation under the newly added section 506(g).¹⁵⁵

A drug or biological product is eligible for RMAT designation if it is a “regenerative medicine” therapy that is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such a disease/condition.¹⁵⁶ Regenerative medicine is defined in the Act as “cell therapy, therapeutic tissue-engineering products, human cell and tissue products, and combination products using any such therapies or products.”¹⁵⁷ The FDA has interpreted this definition to include gene therapies as well as combination products such as biologic-device or a biologic-device-drug product.¹⁵⁸ The benefits of an RMAT designation are similar to the breakthrough therapy designation, including expedited FDA review of the IND application and a flexible interaction process with the FDA to design acceptable endpoint evidence for approval.¹⁵⁹

The RMAT designation is the most relevant expedited program track for optogenetic therapy. Not only does the FDA consider gene therapy eligible under this category, but the discussion of combination products is also particularly pertinent. Optogenetic therapy can be categorized as a “combination product” since it combines gene therapy (i.e., a biological product) with a medical device for light delivery. Furthermore, the nanoparticle method for light delivery falls within the definition of “drug,” but would still require a near-infrared light source for activation (i.e., a

medical device). The potential inclusion of such combination products under RMAT designation means that an optogenetic therapy granted such a designation would be reviewed as one therapy within the same IND application rather than the developer having to submit separate applications, and follow separate regulatory pathways, for each of the biological product, drug, and medical device components of the optogenetic therapy.

D. Priority Review and Accelerated Approval

A product that receives fast track, breakthrough, or RMAT designation may be eligible for priority review, if clinical data supports a “significant improvement in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition.”¹⁶⁰ If priority review is granted, CBER will commit to reviewing the BLA within six months instead of the typical 10-month timeline.¹⁶¹ Accelerated approval is granted when the disease course is long, and an extended period of time is required to measure the clinical benefit of a treatment.¹⁶² The FDA therefore follows a flexible approach to determining whether certain intermediate clinical endpoints are reasonably likely to predict a clinical benefit with meaningful advantages over existing therapies for patients with serious or life-threatening conditions.¹⁶³ After a drug or biological product is granted accelerated approval, the therapy can enter the market but still requires postmarket confirmatory trials to verify the predicted clinical benefit.¹⁶⁴

Optogenetic therapy may therefore qualify for either priority review or accelerated approval depending on the type of disease/condition that the specific therapy is intended for, and the available preclinical and clinical evidence at the time of an IND submission.

PART VI: POLICY IMPLICATIONS

Optogenetic therapy has bigger social and policy implications that go well beyond the issues cov-

ered in the standard regulatory process. The discussion so far has focused on using optogenetic technology as a therapy for serious conditions. This represents the most straightforward first applications of optogenetic technology given the clinical nature of most optogenetic studies in animal models and public support for such uses. Research suggests that there is substantial public support for the use of gene therapy for the treatment and even prevention of disease.¹⁶⁵ Looking into the future, however, optogenetic technology may be contemplated for use beyond medical treatment in biological enhancement for healthy individuals.

Optogenetic enhancement has already been successfully attempted in animal studies. In one example, Liu and colleagues “implanted” false memory into mice using optogenetics.¹⁶⁶ In a classic fear-conditioning experiment, mice learned to associate a specific environmental context with a painful electrical shock, which resulted in freezing behavior upon re-exposure to the same context the following day without any shock, demonstrating a memory for the painful experience in that specific place.¹⁶⁷ When mice were placed in a different environment the following day in which they never received a shock, they didn’t freeze, which showed that their memory was always specific to the environment in which they had a painful experience.¹⁶⁸ In this optogenetic experiment, ChR2 was targeted so it would be expressed only in the specific cells that were active during the learning phase of this fear-conditioning experiment.¹⁶⁹ The following day, after learning, the mice were placed in a new environment — one that was never associated with a shock — and only upon blue light stimulation of those cells that were induced to express ChR2, the mice froze.¹⁷⁰ Therefore, the cells that were involved in learning the fear memory were optogenetically-labeled during learning and could be turned on with light in a completely new environment to reactivate the memory — a false memory since the new environment was not a dangerous one. The ability to turn memory on and off at will with optogenetic technology can be viewed as a form of enhance-

ment that could potentially be used in nondisease states.

Enhancement has been defined in a recent report by the National Academy of Sciences and the National Academy of Medicine as “boosting our capabilities beyond the species-typical level or statistically normal range of functioning” and “a nontherapeutic intervention intended to improve or extend a human trait.”¹⁷¹ The report recommends that gene editing (and by extension gene therapy more generally) should not proceed with enhancement purposes at this time.¹⁷² Likewise, in a recent Pew survey with over 4,000 participants, individuals expressed anxiety over the use of gene therapy and gene editing for enhancement purposes.¹⁷³ Without public support for optogenetic technology with enhancement purposes, it is unlikely that policymakers would support such uses. However, over time, if optogenetic technology improves to become exceptionally safe and much less invasive, public perception towards enhancement may start to shift.

CONCLUSION

In just over a decade after its first experimental use in neurons, optogenetics has gone from a basic research tool for studying brain function to an FDA-authorized treatment in human clinical trials. While many scientific questions of safety and effectiveness remain, regulatory bodies will play an invaluable role in shaping how this technology evolves for medical uses. When contemplating optogenetic applications beyond the clinic, society will determine how much light to shine on optogenetic innovations.

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