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Design of Optogenetic Microimplants for the Treatment of Neurodegenerative Disease

Zhichen Lin

School of Mechanical Engineering, Shandong University, Jinan, China
*Corresponding author: 1812010604@stu.hrbust.edu.cn

Abstract:

In the context of global aging, neurodegenerative diseases such as Alzheimer's disease have become important issues in global public health and scientific research. This is due to their soaring incidence, serious impact on patients' quality of life, and the huge burden they place on families and social economies. However, current treatments, such as drug therapy and deep brain stimulation, have obvious shortcomings. Moreover, there is a lack of precise neuromodulation tools to study the pathogenesis of these diseases In order to solve these problems, optogenetics has attracted attention in recent years, which uses light as a stimulus signal carrier and can realize the detection and control of neurodegenerative diseases at the level of neurons and neural circuits by implanting micro-implants such as μ leds. This review summarize the recent advances in microimplant technology in the fields of optogenetics and neuroscience, and summarize the development and application of optogenetic microimplants for the treatment of neurodegenerative diseases in detail.

Keywords: Optogenetics; microimplants design; neurodegenerative disease.

1. Introduction

Neurodegenerative diseases are a group of irreversible neurological disorders. They are characterized by delayed onset and selective neuronal dysfunction, caused by the loss of neuronal cells in the brain and spinal cord. It mainly includes Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD) [1]. The clinical symptoms of such diseases include cognitive decline and motor dysfunction, often accompanied by psychological and behavioral symptoms. Conventional treatments include drug therapy, deep brain stimulation (DBS), and surgery. However, drug therapy often has slow action and many side effects, while DBS and surgery are invasive procedures with their own limitations. These treatments have a series of shortcomings, including the need to implant invasive electrodes with low spatial resolution, and the inability to accurately locate specific lesion brain areas [2]. As global population aging accelerates, neurodegenerative diseases have emerged as a critical challenge, profoundly impacting both human health and the social economy. Studying the pathogenesis and treatment strategies of neurodegenerative diseases has become one of the important research directions in the field of neurology in recent years.

Spires-Jones TL et al. pointed out that although the histopathological features of various neurodegenerative diseases are not identical, they may share common cellular and molecular mechanisms [3]. Therefore, there is an urgent need for a neuromodulation technology that can accurately regulate physiological processes at the level of neurons and neural circuits, so as to better understand the occurrence and development of such diseases and implement effective treatment [4]. In this context, optogenetics has been proposed and developed. Optogenetics is a pioneering technology that combines optics and genetics. It allows target neurons to express photosensitive ion channels (photosensitive proteins) through genetic modification or injection of modified viruses, and then excifies or inhibits target neurons by specific bands of light signals. Due to its high spatial resolution and relatively low invasiveness, optogenetics has been widely used to analyze the function of specific neurons and neural circuits [5]. At the same time, in order to solve the problems such as the low transfection efficiency of optogenetics virus and the potential tissue damage caused by the implantation of micro-LED arrays, researchers have designed and improved a series of Microelectromechanical Systems (MEMS) for detection, stimulation, and treatment [6]. The use of optogenetic microimplants as auxiliary drug delivery makes the existing optogenetic technology better adapt to the research and treatment needs of neurodegenerative diseases.

This review focuses on the recent progress in the design of optogenetic microimplants for neurodegenerative diseases. This paper began by tracing the evolution of optogenetics

and microimplant technology, exploring their transformative applications in neuroscience research. Then, three promising directions of optogenetic microimplants for the treatment of neurodegenerative diseases are discussed and summarized, respectively: Micro Optical Brain Stimulator, wireless closed-loop optogenetic electronic device and optoelectronic upconversion electronic device. Finally, suggestions and prospects for further promoting the clinical translation of this technology and overcoming current challenges are provided.

2. Optogenetics

Optogenetics is an emerging technology that combines genetics and optics to control cell activity in living tissues through light. Optogenetics implants photosensitive proteins into cells through viral vectors. These proteins act as ion channels, selectively transporting ions under specific light frequencies based on membrane potential, thus activating or inhibiting certain neurons. Optogenetics not only has the advantages of non-destructive, high spatial and temporal resolution, and highly reversible, but also provides solutions to two major problems faced by traditional electrophysiological neural interfaces (namely, unable to achieve inhibitory neural regulation, large stimulation area and uncontrollable target) [7]. In recent years, optogenetics has been widely used in the mechanism research of neuropsychiatric diseases such as Parkinson's disease, epilepsy, autism and so on.

In 1979, Crick proposed that the next key goal of molecular biology was to rapidly and precisely inhibit or activate one or more neurons, so as to study the relationship between neurons and neural circuits and behavior [8]. He pointed out that this carrier could be light, because of its extremely high spatial resolution and timeliness. The theory provides a preliminary basis for optogenetics. The literature also mentions the use of viruses, such as herpes simplex virus, as a tool to tag and trace nerve cells and their connections. This method was also later developed as one of the main ways to implement optogenetics.

In 2005, Boyden expressed ChR2 protein in mammalian nerve cells for the first time and found that blue light accurately activated nerve cells with precise time series, which marks the successful utilization of optogenetic tools to study the behavior of mammalian neurons [9]. Subsequently, a variety of photosensitive proteins were discovered and applied successively, such as channelrhodopsin, ChR, bacterial rhodopsin, and halorhodopsin have all been shown to optically excite or inhibit mammalian neurons (Fig. 1).

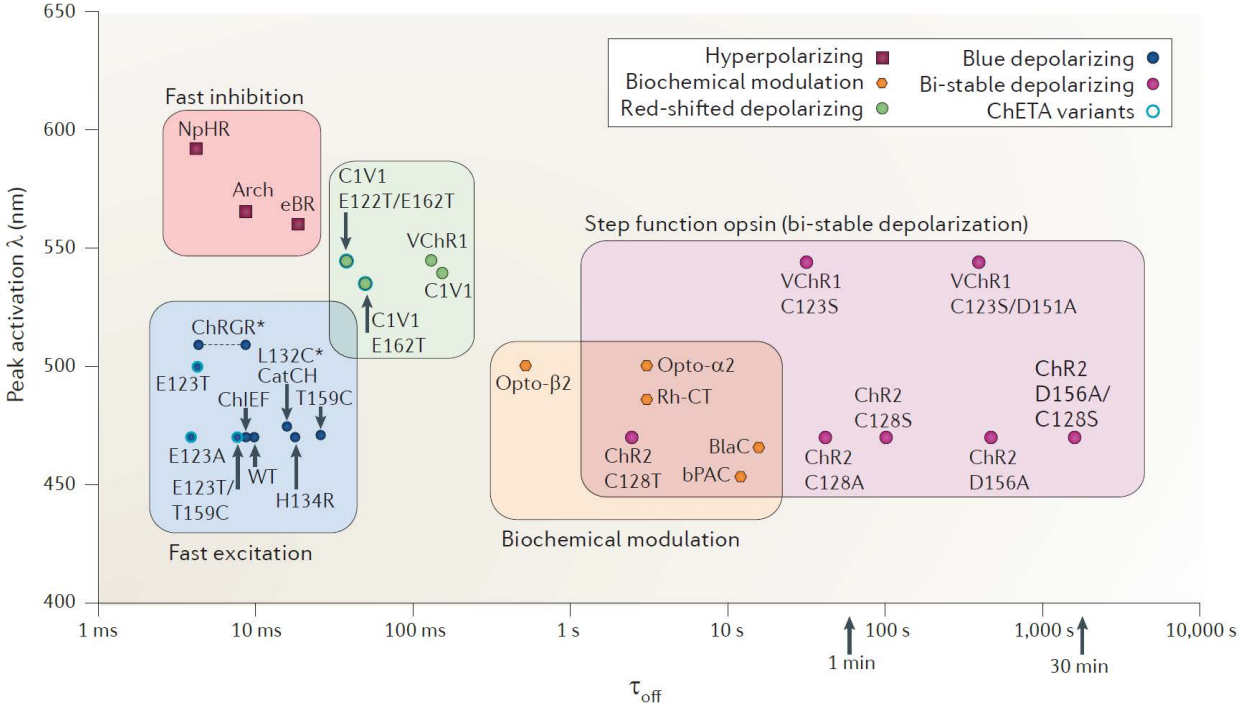

Fig. 1 Characterization and classification of common photosensitive proteins [10].

In recent years, optogenetics, with its high spatial resolution, has provided a new approach to understanding the mechanism and treatment methods of various central nervous system diseases at the level of neurons and neural circuits. For example, researchers have applied this technology to study Parkinson's disease and epilepsy. In order to explore the therapeutic effect of optical inactivation in the subthalamic nucleus (STN), Hyung Ho MS et al.

injected semi-Parkinson's disease rats induced by 6-hydroxydopamine with hSynapsin1-NpHR-YFP adeno-associated virus and an equal volume of phosphate-buffered saline, respectively, and implanted optical fiber into the ipsilateral STN for stimulation three weeks later [11]. Behavioral tests on these rats have shown that optical suppression of STN can significantly improve forelimb dyskinesia caused by 6-hydroxydopamine. Yi Lu et al. used optogenetics to study the seizure propagation principle of temporal lobe epilepsy (TLE) in a transgenic mouse model of VGAT-ChR2 [12]. In order to explore the grid dynamics of TLE affecting pathological circuits in vivo, multi-channel photoelectrode arrays were implanted into multiple brain regions for accurate light stimulation, and local field potentials in dentate gyrus/hippocampus (DGH) and medial temporal cortex (MEC) were recorded by electrophysiological techniques. The results show that during seizures, the abnormal discharge is transmitted from dentate gyrus/hippocampus (DGH) to medial temporal cortex (MEC) through the feedforward propagation pathway, rather than through a re-entrant loop.

3. Applications of microimplants in brain science

Just as optogenetics provides powerful tools for neuroscience research, another important development in this field is the use of microimplants. Microimplants are a class of highly miniaturized medical devices, typically in the um or mm scale, designed to perform a variety of functions within the human body such as monitoring, treatment, and data recording.Based on microelectromechanical system (MEMS) technology, biocompatible design, and wireless communication technology, the micro-implants offer advantages such as miniaturization, low cost, and high precision for clinical treatment. In recent years, micro-implants, especially implantable flexible neural electrodes (IFNEs), have been playing an increasingly important role in brain science and have proposed new solutions to many clinical problems. These devices provide a way to interact directly with the brain and are used in brain-computer interfaces (BCI), drug delivery and other fields.

3.1 Brain computer interface

A brain-computer interface (BCI) is an advanced communication system that establishes a direct connection between the user's brain and external devices, such as computers or prosthetics, enabling direct brain-to-machine interaction.BCIs work by detecting electrical signals from the nervous system and performing feature extraction and classification. This process converts the user's intentions into control signals, enabling communication with the external environment or control of external devices [13]. Some of the microimplants used in BCI include, but are not limited to, deep brain stimulation (DBS) electrodes, Neuropixels probes, and flexible neurotassels.

Deep Brain Stimulation (DBS), a widely used microimplant technique, borrows from the cardiac field. A typical DBS system generally consists of an intracranial electrode, an extension cord, and a pulse generator [14]. Schiff et al. reported the progress of a phase this paper clinical study on the use of an electrostimulation implant in msTBI patients [15]. The results found that DBS electrodes significantly improved cognitive ability and attention in patients with traumatic brain injury, and in cognitive tests after three months, the five subjects who received DBS showed a 15 percent and 52 percent improvement in information processing speed. In 2019, Neuralink developed a thousandchannel recording system based on flexible microfilament electrodes, which uses a surgical robot to automatically implant 96 polyimide microfilament electrodes into the mouse cortex with the help of rigid microneedles [16]. Each microfilament contains 32 recording sites. As a result, the total number of channels reached 3072. This unprecedented number of recording sites provides a complete solution for large-scale electrophysiological recording, enabling more comprehensive brain activity monitoring.

3.2 Drug delivery

Drug delivery to the central nervous system plays a crucial role in the treatment of central nervous system diseases. The main challenge is that the central nervous system is highly protected by physiological barriers, the Blood-brain Barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB). They are highly selective about the molecules that enter and exit the nervous system, tightly controlling the chemical composition of the brain, which blocks the entry of most drug molecules. In addition, taking anti-tumor drugs as an example, most anti-tumor drugs of the nervous system have poor water solubility, short half-life and lack of selectivity [17]. After oral or intravenous injection, it can only enter cells through free diffusion, which may cause cytotoxicity to both target cells and normal cells.

To address these challenges in drug delivery to the central nervous system, researchers have turned to innovative solutions. One promising approach is the use of micro-implants. Micro/nanomaterials can use their biological properties or physical means (such as magnetic fields, electric fields, light fields) to carry large doses of drugs across physiological barriers. At the same time, nanorobots based on MEMS can navigate and operate precisely in the body, thus greatly improving the accuracy and efficiency of drug delivery [18]. LIU Y et al proposed a microneedle patch

with the expression of vascular endothelial growth factor (VEGF) in the intracranial based on adeno-associated virus (AAV) [19]. The microneedles are composed of gelatin methacryloyl (GelMA), which can degrade in the brain and is coated with AAV. After implantation in ischemic brain tissue, microneedles can ensure the spatial accuracy of AAV delivery, and through slow degradation and release of AAV, the expression of VEGF has been shown to significantly increase the area and length of blood vessels in ischemic areas and the number of new endothelial cells in subsequent imaging observations. H Zhang et al. created neutrobots, a dual-response bio-hybrid micro-robot for active targeted drug delivery in vivo [20]. It consists of neutrophils that engulf nanogels, containing hydrophobic Fe3O4 nanoparticles (Fe3O4 NPs) and the model anti-cancer drug paclitaxel (PTX). With the magnetic response properties of Fe3O4 NPs and the chemotaxis of neutrophils, neutrobots are able to respond to external magnetic fields (to control their movement within blood vessels) and inflammatory factor gradients (to penetrate the BBB and locate the site of inflammation or pathology). Experiments have shown that neutrobots can efficiently and precisely locate the site of inflammation and release drug-loaded nanogels under specific conditions, such as when receiving PAM stimulation signals. This targeted drug delivery approach has been demonstrated to greatly inhibit the proliferation of tumor cells.

4. Design of optogenetic micro-implants for the treatment of neurodegenerative diseases

Neurodegenerative diseases, including Alzheimer's disease (AD), Huntington's disease (HD), and Parkinson's disease (PD), are a group of conditions that affect the brain and other parts of the central nervous system. Neurodegenerative diseases are related to many factors such as heredity, environment and aging. The main cause of neurodegenerative diseases is the loss of neurons in the brain and spinal cord, and functional deterioration occurs over time, resulting in dysfunction [21]. The clinical manifestations are generally: muscle stiffness, slow movement and tremor, autonomic nervous dysfunction, mental disorders. While these diseases typically affect the elderly, recent years have seen an increasing trend of earlier onset in younger populations [22].

At present, the treatment of neurological diseases is mainly through medication. Taking Parkinson's disease as an example, the main drugs currently used include levodopa (L-DOPA), catechol-O-methyltransferase (COMT) inhibitors, and dopamine agonists, among others.However, drug treatment is usually accompanied by obvious side effects, such as levodopa and other dopamine receptor agonists may cause hallucinations, amantadine may cause edema of lower limbs or ankles. COMT inhibitors such as tocapone may be hepatotoxic. In recent years, DBS has been gradually applied in the treatment of neurological diseases, but due to its low spatial resolution, it cannot accurately locate the target cells, and long-term implantation of electrodes is easy to cause inflammation and chronic foreign body reaction in brain tissue, which limits its clinical application [23]. The emergence of optogenetics allows researchers to study the pathogenesis of neurological diseases at the level of neurons and neural circuits, as well as to develop new diagnostic and treatment approaches. Ultimately, this technology is expected to achieve non-invasive and high-precision deep brain stimulation methods without surgery. Current research on optogenetic micro-implants is mainly focused on miniaturization, wireless, multi-mode and non-invasive. Through the design and optimization of micro-implant design, it is conducive to further improving the effectiveness of optogenetics in the treatment of neurological diseases.

4.1 Micro Optical Brain Stimulator

As a direct means of optogenetic stimulation of the brain, implantable photoelectric hybrid probes have developed rapidly in recent years. Common means of optical stimulation usually include optical fiber, on-probe μLED-s and waveguide-based approaches [24]. In order to improve biocompatibility, increase stimulation sites and reduce surgical trauma, micro optogenetic implants have made a lot of progress in recent years.

Naughton J R et al. developed an optogenetic microelectrode array that can be used to study neural networks in the brain, Shielded Coaxial Optrode Arrays [25]. To address the electrical crosstalk issue caused by increased electrode array channel density, the researchers proposed a novel coaxial electrode architecture. This design not only mitigates the crosstalk problem but also integrates optical stimulation functionality, serving as both an optical waveguide and a shielding electrode. As shown in the Fig. 2, the inner layer of metal serves as the coaxial core and the outer layer serves as the shielding layer. Through the shielding layer, the electrical crosstalk between electrodes is reduced, so as to improve the spatial resolution of the electrode array. At the same time, the inner metal micro/nanowire not only transmits the electrical signal, but also acts as a light waveguide to guide the light signal to the specified nerve cell. All in all, this architecture simultaneously integrates electrophysiological recording and light stimulation functions into a micro-implant, which is of great significance for accurate detection and stimulation of neural networks.

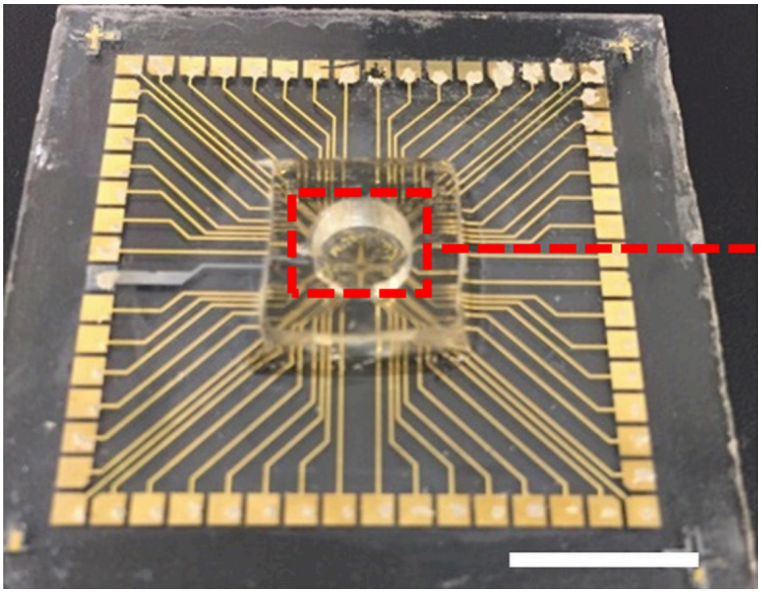

Fig. 2 Coaxial microelectrode array (cMEA) on glass substrate. Scale bar: 10 mm [23].

Zou, L et al. developed an innovative optrode system for precise integration of optogenetics and brain electrophysiology [26]. This system features self-assembly properties and is delivered by viral vectors. As shown in the Fig. 3, the system consists of flexible microelectrode filaments and optical fibers consisting of 33 channels of 100 nanometer-thick gold microelectrodes distributed on polyimide (PI) filaments 3 microns thick, 12 microns wide and 4.5 millimeters long. The microelectrode filaments and optical fibers were self-assembled in a polyethylene glycol (PEG) carrier delivered by a nanoscale viral vector. The self-assembly process utilizes capillary action to ensure close alignment and fixation of the microelectrode and fiber within the PEG carrier. PEG gradually dissolves and degrades in the extracellular space of the brain after implantation, releasing adenovirus vectors carrying light-sensitive protein genes that allow light to stimulate and excite specific neurons and simultaneously perform multi-channel extracellular recording via microelectrode filaments. Experimental results show that the system can significantly improve the accuracy of electrophysiological recording and optogenetic control of neuron population (92%). The small size and flexibility of the microelectrode also reduces the mechanical mismatch with the tissue and the inflammatory response caused by fretting.

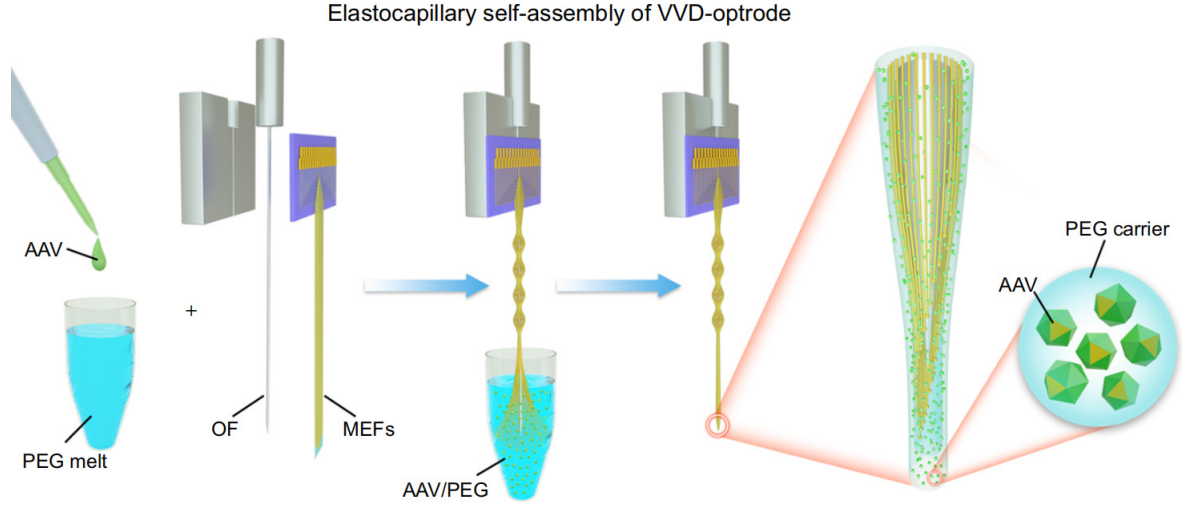

Fig. 3 To construct a VVD-optrode, an adeno-associated virus (AAV) vector solution was added in a molten PEG (MW 4000). An optrode, consisting of a MEF array aligned with an optical fiber (OF), was immersed in the molten AAV/PEG mixture and progressively withdrawn into the ambient air [26].

4.2 Wireless closed-loop optogenetic electronics

In recent years, optogenetics technology has been developing towards intelligent closed-loop regulation. Traditional optogenetic microimplants use laser and fiber connections to stimulate specific neurons and neural circuits. However, their large size and wired connection mode restrict behavior-related research, particularly studies involving animal movement and posture [27]. In order to reduce the invasiveness as much as possible and improve the naturalness and authenticity of the experiment, wireless closed-loop optogenetic electronic devices have become a popular design direction.

Ausra J et al. have developed a wireless, battery-free, subcutaneous implantable platform for transcranial and long-range optogenetic studies in freely moving animals [28]. As shown in the Fig. 4, the device consists of a flexible circuit, a miniature light-emitting diode (mu-ILED), a capacitive energy storage unit, and an antenna for wireless energy transmission. Magnetic resonance coupling is used to achieve wireless transmission of energy, receiving energy from an external coil through a small antenna. μ-ILED can emit different wavelengths of light to meet the need to stimulate specific photosensitive proteins. In terms of energy storage, the platform uses ceramic capacitors with high energy density to build capacitor banks by connecting multiple capacitors in parallel, gaining the ability to store relatively large amounts of energy in a very small volume. This capacitor bank design, combined with digital power management technology, enables the platform to deliver peak power during μ-ILED activation while efficiently storing energy during idle periods. In addition, the device uses Pyralux AP8535R as the substrate material of the flexible circuit, and is mechanically designed to be as thin and flexible as possible, so that it can better fit the animal skull. Experiments show that the platform can achieve precise optogenetic control of the deep brain region of animals while minimizing the disruption of surgery and interference with the behavior of the tested animals.

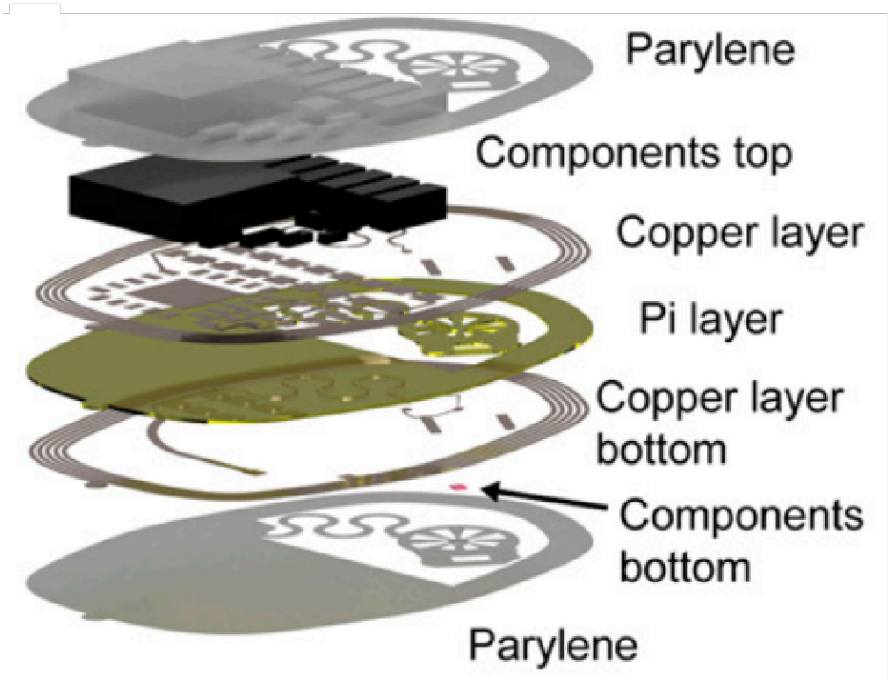

Fig. 4 Rendering of device layer structure [28].

Ouyang, W et al developed a wireless, battery-free implantable multimodal closed-loop neuromodulation system for small animals [29]. This system allows autonomous recording of electroencephalography (EEG), electromyography (EMG), and body temperature without physical restraints or batteries. It utilizes optogenetics and pharmacology as means of neuromodulation. Closed-loop neural adjustment based on inherited deep learning algorithms. As shown in the Fig. 5, the system includes electrodes for neurorecording, a micro-light-emitting diode (μILED) probe for neuromodulation, a drug delivery device, and a system-on-a-chip (SoC) integrated with a Bluetooth Low Power (BLE) module and a deep learning module. The power supply adopts the near field communication (NFC) frequency of 13.56MHz for magnetic induction coupling to realize wireless energy supply. The experimental results show that the system is equivalent to the wired system in the recording of EEG and EMG, the wireless continuous

transmission data sampling rate is 1HZ, and shows excellent long-term stability (stable operation for at least six weeks in animal models), and successfully realized the programmable closed-loop drug suppression of epilepsy by EEG feedback.

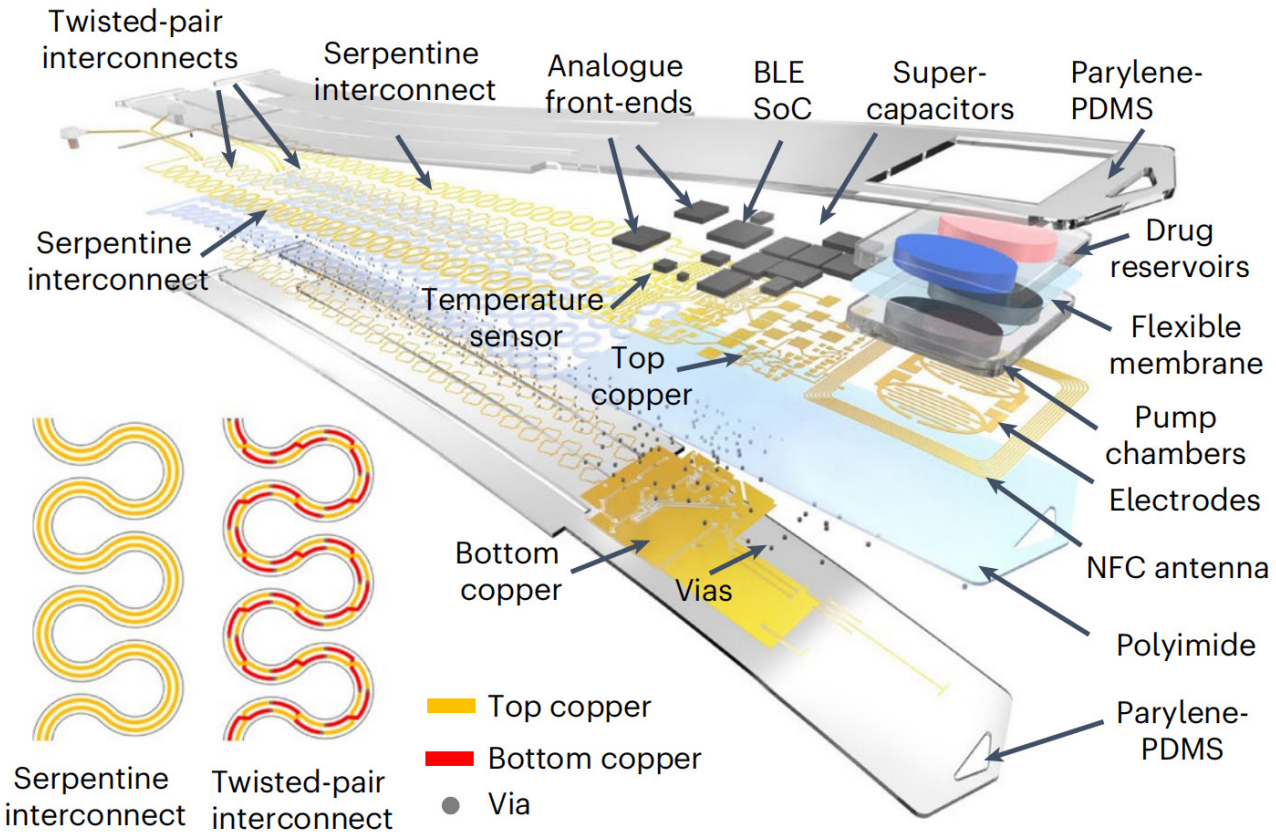

Fig. 5 Layered schematic illustration of the device [29].

4.3 Photoelectric upconversion electronic devices

Optogenetics relies on photons to manipulate cellular and subcellular processes. However, the biggest challenge at present is the need to implant light-transmitting optical fibers in living organisms, as current photosensitive proteins can only be activated by visible light, which cannot effectively penetrate multiple layers of biological tissue [30]. In order to solve this problem, photoelectric upconversion electronic devices have received more and more attention in recent years. Upconversion luminescence refers to a phenomenon where a material, when excited by low-energy (long-wavelength, low-frequency) light, emits high-energy (short-wavelength, high-frequency) light. This process is also known as anti-Stokes luminescence. In 1966,Auzel discovered that rare-earth element doped sodium ytterbium tungstate glass emits visible light or 800nm near-infrared light under the condition of near-infrared laser (usually 980nm) excitation, which formally proposed the idea of “up-conversion luminescence”. Up-conversion materials utilize the feature that near-infrared light falls within the transparent window band of biological tissues, allowing it to penetrate deep tissues. By converting near-infrared light to visible light, these materials can activate photosensitive proteins, thus enabling non-invasive optical regulation of deep tissues [31].

He Ding et al. proposed a new type of optoelectronic semiconductor heterostructure and developed a highly integrated, micron-scale micro-implantable device [32]. This device successfully achieved wavelength up-conversion from near-infrared to visible light across various bands from near-infrared light to visible light. As shown in the Fig. 6, the up-conversion device has a size of 220×220 microns ² and an active layer thickness of 9 microns. It is based on a fully integrated micro-scale photoelectric device, using photovoltaic diodes (PDs) to capture low-energy infrared photons to provide photoelectric current, thereby driving light emitting diodes (leds) to emit high-energy visible photons, realizing the up-conversion of nearly infrared light (about 810 nm) to visible light (630 nm red or 590 nm yellow). The quantum yield is about 1.5%. In biological experiments, the device was implant-

ed into different subcutaneous areas in mice and rats, and no significant inflammatory response was observed over a period of up to three weeks, and the upconversion ability was maintained. This study provides a new research idea for the realization of low-trauma, wireless, implantable photoelectric neural interface.

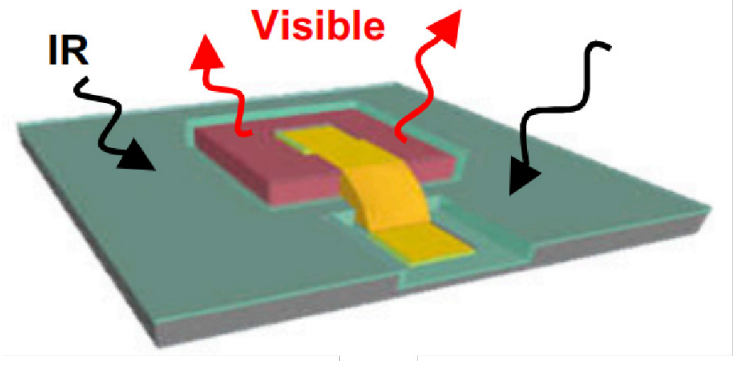

Fig. 6 Schematic illustration of the fabricated upconversion device [30].

Wang Y et al. developed a flexible, fully implantable upconversion device for epidural spinal cord stimulation [33]. As shown in the Fig. 7, the device is capable of converting near-infrared (NIR) radiation to visible light for optogenetic manipulation of spinal cord tissue. It uses biocompatible thermoplastic polypropylene as a skeleton, mixed with up-conversion nanoions (UCNPs), to make a flexible optoelectronic up-conversion device with a diameter of approximately 500 microns and weighing less than 1 mg. A photoelectrode device implanted in the L4 vertebral body can reliably trigger hind limb muscle activity via NIR trigger and is recorded by electromyography (EMG). In addition, within four months of the experiment, the device showed excellent long-term biological compatibility, with virtually no inflammatory response around the implant. In open-field testing, ChR2 transgenic mice with a functional UCNP-device showed significantly reduced mobility. This suggests that the NIR-triggered implanted photoelectrode successfully modulated the animal's motor behavior.

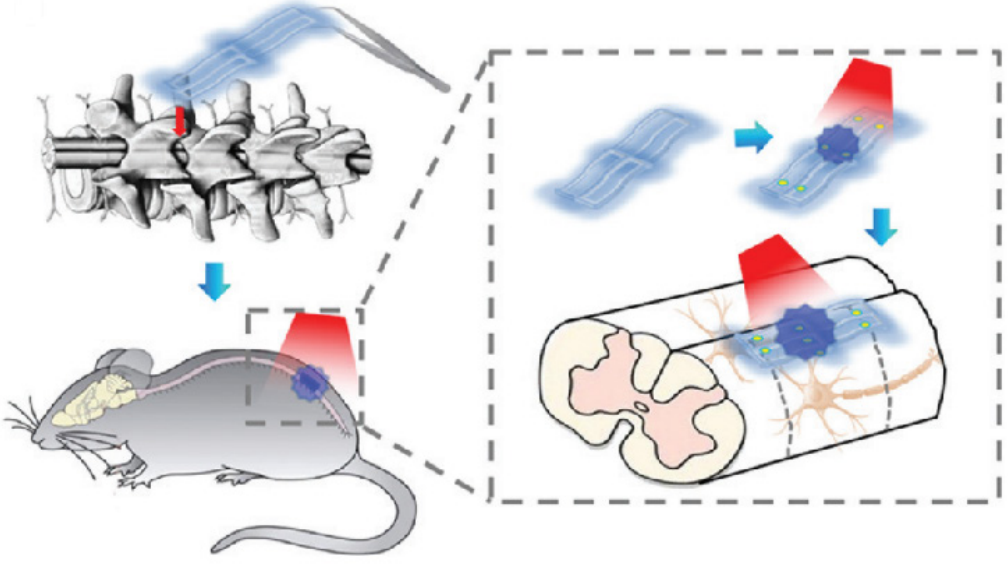

Fig. 7 Diagram of implantation of the UCNP-PP-optrode at the spinal cord of a mouse by minimal invasive surgery. The mouse was first transfected with the optogenetics virus at the L4 lumbar vertebra. After recovery, UCNP-PP-optrode was implanted and the surgical site was covered with an artificial PDMS skin to allow efficient NIR delivery [33].

5. Conclusion

The development of microelectromechanical technology and the continuous improvement of optogenetics have greatly benefited optogenetic microimplants. As a result, these devices have made significant progress in accurate detection, neural network stimulation, and drug delivery. It is expected that optogenetic microimplants will become

one of the important research and treatment methods for neurodegenerative diseases in the future. Despite the efforts of researchers, optogenetic microimplants have been widely used in animal behavioral experiments, but there are still some problems such as low viral transfection efficiency, low photoelectric conversion efficiency leading to obvious thermal effect, insufficient tissue penetration, and poor biocompatibility, which limit their further clinical application. In order to overcome these problems, optogenetic micro-implants should be developed towards miniaturization, wireless, closed-loop control, and overcome the poor propagation ability of visible light in brain tissue by up-conversion luminescence technology. Meanwhile, other standardized optogenetic devices, such as fluorescence microscopy with higher resolution, should also be developed to better adapt to future research needs. Although the application of optogenetic microimplants in studying neurodegenerative diseases is still in its infancy, optogenetics will soon offer breakthrough solutions for addressing the challenges posed by these conditions.

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