

# Bioelectronic Implants for Nerve Regeneration: Materials, Mechanisms, and Therapeutic Strategies

Haoran Sun

Zonglian College, Xi'an Jiaotong University, Xi'an, China

1628643532@qq.com

**Abstract.** Nerve regeneration remains a major clinical challenge, particularly within the central nervous system, where repair capacity is limited. Bioelectronic implants offer a promising therapeutic approach by integrating electrical stimulation with biocompatible materials to enhance axonal growth, glial support, and neurotrophic signaling. This paper reviews the mechanisms underlying nerve repair—including axonal regeneration, glial cell function, extracellular matrix remodeling, and neural stem cell applications—and explores how bioelectronic devices modulate these processes. Recent advances such as flexible electrodes, wireless and self-powered systems, and optogenetic interfaces have expanded the capabilities of neural modulation with improved precision and biocompatibility. Clinical applications in spinal cord and peripheral nerve injury are discussed, alongside challenges such as long-term biocompatibility, ethical considerations, and translational barriers. Future directions emphasize interdisciplinary integration and the development of intelligent, adaptive neural interfaces

**Keywords:** Bioelectronic implants, Nerve regeneration, Electrical stimulation, Neural interfaces.

## 1. Introduction

Nerve regeneration is a major challenge in the field of nerve injury treatment, especially in the central nervous system, where the ability of neurons to regenerate is extremely limited. With the progress of science and technology, nerve regeneration has not only made an important breakthrough in basic research, but also gradually become the key to solve nerve injury and neurodegenerative diseases in clinical practice. Although there are a variety of nerve repair methods, such as drug therapy<sup>[1]</sup>, gene therapy<sup>[2]</sup>, and cell transplantation<sup>[3]</sup>, many of them still face the challenge of poor effect and treatment persistence due to the complexity of nerve tissue and some obstacles in the repair process.

In recent years, as a revolutionary method, electron implantation technology has gradually made some progress in the field of nerve repair. This technique uses electronic devices to promote the functional recovery of nerve cells through electrical stimulation or signal transduction, providing a more accurate and efficient treatment option compared with traditional nerve repair methods. Electron implantation technology not only breaks through physical barriers, but also enables long-term and adjustable nerve stimulation, thus providing a new treatment idea for nerve regeneration.

This article reviews the application and mechanism of electron implantation in the field of nerve regeneration, and explores how electron implantation promotes the process of nerve tissue repair and regeneration. By analyzing the research status and clinical application of electron implantation, this article reviews the methods of nerve regeneration.

## 2. The basic principles of electronic implantation and nerve regeneration

### 2.1 nerve regeneration

Neural regeneration is a complex process involving multiple cellular and molecular mechanisms. This process encompasses axonal regeneration, the role of glial cells, the influence of extracellular matrix, the participation of neural stem cells, and the regulation of signaling pathways, among other aspects.

### 2.1.1 Axonal regeneration

Axonal regeneration is a crucial step in the process of nerve repair. Axonal regeneration is associated with a significant gene and gene family<sup>[4]</sup>. In peripheral nerves, axons can start to regenerate after injury through the formation of axonal growth cones. The formation of axonal growth cones depends on the reorganization of microtubules and actin<sup>[5]</sup>, and these changes convey growth factors and signals within the cell, promoting axonal extension. Growth factors such as nerve growth factor (NGF)<sup>[6]</sup> and brain-derived neurotrophic factor (BDNF)<sup>[7]</sup> directly affect axonal growth and regeneration. However, in the central nervous system, the ability of axonal regeneration is relatively weak, which is related to the demyelination of axons, the formation of glial scars at the axonal terminals, and inhibitory molecules in the neural environment<sup>[8]</sup>.

### 2.1.2 Role of Glial Cells

During the process of nerve regeneration, glial cells play a crucial role<sup>[9]</sup>. Schwann cells play a dominant role in the regeneration of peripheral nerves, as they promote axonal recovery by forming myelin sheaths<sup>[10]</sup>. Meanwhile, astrocytes and oligodendrocytes also have significant roles in the repair of the central nervous system. Astrocytes not only participate in the repair process but also regulate the environment for nerve regeneration by secreting cytokines. Oligodendrocytes play a role in axonal regeneration by promoting the regeneration of myelin sheaths<sup>[11]</sup>.

### 2.1.3 Effects of Extracellular Matrix

The extracellular matrix plays a supporting and guiding role in neural regeneration<sup>[12]</sup>. Components such as laminin<sup>[13]</sup> and fibronectin<sup>[14]</sup> in the matrix provide necessary support for the regeneration of neurons. Moreover, matrix metalloproteinases (MMPs) play an important role in the remodeling of the extracellular matrix, as they promote neural regeneration by degrading specific matrix components<sup>[15]</sup>. In the repair of peripheral nerve injuries, the application of biodegradable nerve conduits, such as those based on decellularized exogenous extracellular matrix materials, can provide better support and environment for neural regeneration<sup>[16]</sup>.

### 2.1.4 The Role of Neural Stem Cells

Neural stem cells possess potential for repair during the process of neural regeneration. They can differentiate into neurons and glial cells, and also regulate the surrounding environment by secreting neurotrophic factors, promoting the repair of damaged areas<sup>[17]</sup>. In clinical applications, the transplantation of neural stem cells is used to treat diseases such as spinal cord injury, and it has a positive effect on axon regeneration and the recovery of neural connections. It is shown in Table 1.

Table 1. Summarizes of The Role of Neural Stem Cells

Article Title	Author(s)	Year	Main Content Summary
Neural stem cells: developmental mechanisms and disease modeling	Zhao X, Moore D[18]	2018	NSCs give rise to all CNS cell types during development and persist in adults in small numbers, supporting neural plasticity and regeneration. They first produce neurons and then glia during development. Due to limited endogenous NSCs, iPSC-derived NSCs are explored for therapy, though "several challenges remain" (e.g. safety, manufacturing).
Therapeutic role of neural stem cells in neurological diseases	Yang L et al. [19]	2024	This review highlights NSC repair functions: NSCs can self-renew and differentiate to replace lost neurons/glia, and they provide neuroprotection, promote axonal regeneration and remyelination, secrete neurotrophic factors, and modulate the

---

The roles and applications of neural stem cells in spinal cord injury repair	Guo W et al. [20]	2022	injury environment. The authors cite promising outcomes in models of SCI, ALS, and PD, but note challenges including controlling differentiation, limited cell sources, and risks such as tumorigenesis from grafted cells. NSCs are multipotent: they differentiate into neurons and neuroglia, making them well-suited for SCI repair. Transplanted NSCs survive in lesions, fill cavities, and enable host axons to grow across injuries. They also constitutively secrete neurotrophic factors (e.g. GDNF, BDNF) that support axonal and vascular growth in the injured spinal cord. The review covers NSC sources, preclinical evidence and clinical trials in SCI models.
Neural stem cells for Parkinson's disease management: Challenges, nanobased support, and prospects	Oz T, Kaushik A, Kujawska M[21]	2023	This review covers NSC therapy in PD. NSCs' self-renewal and multipotency enable generation of dopaminergic neurons for potential cell replacement. Fetal NSC grafts in PD models showed some symptom improvement but also issues (e.g. grafts developing pathology). NSC therapies face hurdles at every stage (cell preparation, graft survival, integration). The authors discuss combining NSCs with supportive nanomaterials and gene therapies to enhance outcomes.
Stem cell treatments for amyotrophic lateral sclerosis (ALS): A critical overview of early phase trials	Goutman SA et al. [22]	2019	This overview reviews early human trials of stem cell therapies (including NSCs) for ALS. It reports modest functional improvements in some cases, but disease progression generally continued. The authors emphasize the need for powered, controlled trials to determine the optimal cell type, dose, delivery route, and timing, and to address ethical and safety issues (e.g. invasive procedures, patient consent) in ALS cell therapy.
Induced pluripotent stem cell-derived neural stem cell therapies for spinal cord injury	Lee-Kubli CA, Lu P[23]	2015	This review proposes using autologous iPSC-derived NSCs for SCI to overcome ethical and immune issues of fetal/ESC sources. It notes that fetal/ESC-NSC grafts can form neuronal relays in SCI models but require immunosuppression. iPSCs from adult cells provide an ethically acceptable, patient-specific NSC source, enabling autologous transplants. The authors point out that ensuring graft safety (avoiding tumors) and improving differentiation/integration remain key challenges.

---

### 2.1.5 Regulation of Signal Pathways

The biological mechanisms of nerve regeneration are regulated by multiple signal pathways. The Wnt/ $\beta$ -catenin pathway, mTOR pathway and Notch pathway play significant roles in axonal regeneration and repair. The Wnt/ $\beta$ -catenin pathway regulates nerve regeneration by promoting the proliferation and differentiation of nerve cells<sup>[24]</sup>. The mTOR signaling pathway exerts regulatory

effects during nerve regeneration by regulating cellular metabolism and growth to promote axonal regeneration<sup>[25]</sup>. The activation of the Notch signaling pathway helps to inhibit the formation of glial scars, providing a more favorable environment for nerve regeneration<sup>[26]</sup>.

Through these underlying biological mechanisms, neuronal regeneration can be achieved. Moreover, electronic implant technologies enhance the repair and regeneration of neural tissues by modulating specific signaling pathways, offering a more precise and controllable therapeutic approach.

## **2.2 electronic implantation**

### **2.2.1. Basics of Bioelectronics: The Relationship between Electrical Stimulation and Neural Responses**

Electrical stimulation plays a crucial role in nerve regeneration. By precisely regulating the current intensity, frequency and waveform, electrical stimulation can promote the proliferation, differentiation and axonal growth of nerve cells. Studies have shown that appropriate electrical stimulation helps activate the release of nerve growth factors and enhance the nerve repair process<sup>[27]</sup>. For instance, low-frequency electrical stimulation has been proven to promote the regeneration of peripheral nerves. A study summarized the research progress of electrical stimulation promoting peripheral nerve regeneration, summarized the electrical stimulation parameters in preclinical experiments, and discussed its impact on nerve regeneration<sup>[28]</sup>.

Electrical stimulation also has significant effects on the electrophysiological characteristics, cellular signal transduction, and neuronal regeneration of neurons. By regulating the energy metabolism and internal environment stability of neurons, electrical stimulation can enhance the anti-injury ability of neurons and promote neuronal regeneration<sup>[29]</sup>.

### **2.2.2. The development and selection of biocompatible materials**

The success of electronic implant devices depends on the biocompatibility of the selected materials. In recent years, researchers have developed various new materials to meet the requirements of implantable electronic devices for biocompatibility and mechanical compatibility. For instance, the research group led by Zhang Ye from Nanjing University designed an implantable zinc-oxygen battery, which demonstrated excellent electrochemical performance and biocompatibility, and could be integrated in situ on nerve conduits to promote nerve regeneration through electrical stimulation<sup>[30]</sup>. Another study by the University of Cambridge reviewed the challenges and progress in material selection and manufacturing in the field of implantable electrodes, and proposed new materials and manufacturing methods to better interface with biological tissues.

When choosing biocompatible materials, several factors need to be considered, such as their mechanical properties, electrical conductivity, degradability, and interactions with neural tissues. Although traditional electronic materials are not easily regarded as biodegradable, several strategies have been developed to design electroactive and biodegradable material systems: (1) conductive materials mixed with biodegradable components, (2) molecular engineering conjugated polymers with biodegradable parts, (3) naturally derived conjugated biopolymers, and (4) water-soluble metal with encapsulation layers<sup>[31]</sup>.

## **3. The cutting-edge technology of electronic implantation techniques**

### **3.1 High-resolution neural interface**

Recent advances in neural interface design integrate ultrathin flexible implants, high-density 3D-printed microelectrode arrays, and dry microneedle electrodes to create soft, dense, and minimally invasive systems capable of stable, high-resolution neural recording and modulation.

### 3.1.1. Flexible electrode implant

The neural interface probe is located between the nervous system and the implanted electronic device to obtain information about the complex neuronal activities and to reconstruct the damaged neural connections. The main problems currently encountered stem from the material differences between the neural interface probe and the neural tissue. These differences can lead to local immune responses and scar cells to form

near the interface. Therefore, to solve this problem, the design of the neural interface should be very soft to reduce the boundaries between the biological system and the non-biological system. The soft materials of the neural interface have been extensively studied to improve the interface and long-term signal transmission. The design and manufacture of micro and nano devices have greatly reduced the stiffness of the probe and enabled single-neuron measurement<sup>[32]</sup>.

Relevant experiments have developed a kind of flexible and high-resolution thin film (TF) electrode for recording the neural activities of animals and humans. This electrode array is fabricated using standard flexible printed circuit manufacturing techniques and employs biocompatible materials such as liquid crystal polymers, metals, medical-grade silicone and nylon casings<sup>[33]</sup>.

### 3.1.2. High-density microelectrode array

The microelectrode array allows recording vital electrophysiological brain activity but lacks customizable layouts and suffers from limited coverage, fragility, and high cost. Utilizing 3D nanoparticle printing, flexible 3D multi-electrode devices can be fabricated with high density (2600 channels/cm<sup>3</sup>), minimal tissue damage, configurable handle lengths and layouts, and low channel impedance, enabling targeted, large-scale whole-brain signal recording<sup>[34]</sup>. High-density microelectrode arrays also detect jump conduction in peripheral neurons: by coculturing rat sensory neurons with Schwann cells and applying optogenetic stimulation, axonal conduction segments—including high-speed, low-amplitude sections—are recorded electrophysiologically and confirmed via myelin protein immunofluorescence. Spatiotemporal analysis reveals speeds over 2 m/s and increased electrical synapses at segment ends, indicating myelinated jump conduction<sup>[35]</sup>.

## 3.2 Wireless and energy self-supply technology

Modern implantable neural interfaces combine wireless power transmission and on-board biomechanical energy harvesting via piezoelectric nanogenerators to enable autonomous, untethered operation with sustained, high-resolution monitoring and therapy.

### 3.2.1 Wireless power supply implantable device

Since the 1950s, wireless technology has been incorporated into implantable devices. Through remote data collection and control of implantable devices, these wireless technologies have helped researchers and clinicians better understand diseases and improve medical care. Nowadays, the application of wireless technology in some clinical implantable devices is still limited<sup>[36]</sup>. The latest developments and standardization of wireless technology provide a good opportunity for wider use in other types of implantable devices, which will greatly improve the outcomes of many diseases or injuries.

Among them, Wireless Power Transmission (WPT) systems have become a power supply solution for advanced multifunctional microelectronic devices, such as those in current biomedical implants. However, the size of WPT systems, the separation distance between the external environment and the implanted medical devices in the body, the operating frequency caused by power dissipation, and the safety of tissues are key parameters that need to be considered in the design of WPT systems. There are many methods for transmitting wireless power in implanted medical devices (IMD), including capacitive coupling, inductive coupling, magnetic resonance coupling, and recently acoustic and optical power methods<sup>[37]</sup>.

### 3.2.2 Self-powered implantable device

One of the recent innovations in the field of personalized healthcare is the piezoelectric nanogenerator (PENG) for various clinical applications, including self-powered sensors, drug delivery, tissue regeneration, etc. This innovation is believed to have the potential to address some unmet clinical needs, such as the limited lifespan of implanted biomedical devices (e.g., pacemakers) and the associated complications of replacement. For this reason, generating green energy from biomechanical sources for wearable and implantable bioelectronic devices has attracted considerable attention in the scientific community.

The emergence of piezoelectric materials has led to many breakthroughs. Particularly, in the applications of piezoelectric energy harvesting, piezoelectric materials (ceramics, polymers) and piezoelectric nanogenerators, such as self-powered sensors, self-powered pacemakers, deep brain stimulators, etc. Piezoelectric nanogenerators (PENGs) have made significant breakthroughs in transforming implantable medical devices through self-powered sensors, drug delivery systems and tissue regeneration<sup>[38]</sup>.

## 3.3 Integration of optogenetics and optical technologies

### 3.3.1 Optogenetic interface

Optogenetic BMI combines optogenetics and brain-machine interfaces, using photoreceptive proteins to modulate neuronal activity with high temporal/spatial resolution and cell specificity in real time<sup>[39, 40]</sup>. It shows promise in controlling prostheses and treating neurological disorders by adjusting neural activity<sup>[39]</sup>. Advances in hardware—such as micro-ECoG devices that integrate electrophysiological recording and optical stimulation—and closed-loop algorithms that tailor light parameters to ongoing neural signals have improved integration, biocompatibility, and regulatory precision<sup>[41]</sup>, though challenges remain in protein stability, stimulation safety, and ethics<sup>[39]</sup>. Looking ahead, integrating artificial intelligence and functional imaging could yield breakthroughs in neurorehabilitation and brain-brain interfaces<sup>[39, 40]</sup>.

### 3.3.2 Optoelectronic hybrid implant

Hybrid photonic–electronic implants combine optogenetic stimulation (using photosensitive opsins like channelrhodopsin) with electrophysiological recording to enable bidirectional control of neural activity. Early devices suffered from photonic artifacts that compromised recording accuracy<sup>[42]</sup>, but recent material and design innovations have markedly improved performance. For example, a fully biodegradable, flexible hybrid system optimized light paths and minimized artifacts to achieve efficient optical stimulation and reliable recording<sup>[43]</sup>, while a polymer-based, microfabricated implant demonstrated deep-brain stimulation with light loss as low as 4.04–4.4 dB/cm at 670 nm<sup>[44]</sup>. Hardware design now prioritizes spatial precision, biocompatibility, and low invasiveness: flexible, biodegradable implants adhere closely to cortical surfaces, support multi-channel interfaces, and eliminate the need for removal surgery<sup>[43, 44]</sup>. These advances enable high-resolution, closed-loop neural regulation—one study implanted a flexible photonic device in transgenic mice to stimulate sensory regions and record local field potentials concurrently<sup>[43]</sup>—and hold promise for treating epilepsy, Parkinson's, and other disorders, as well as for brain–computer interfaces (e.g., prosthetic control, neurorehabilitation)<sup>[44]</sup>. Nonetheless, clinical translation requires addressing long-term implant stability and developing personalized designs, potentially guided by neuroimaging data.

## 3.4 Medical application

### 3.4.1 Brain-Computer Interface (BCI)

Brain-computer interface (BCI) is a rapidly evolving multidisciplinary technology that enables direct communication between the brain and external devices by acquiring and processing neural signals such as EEG to assist individuals with severe motor disorders<sup>[45, 46]</sup>, with platforms like BCI2000 lowering development barriers and facilitating systematic research across neuroscience,

signal processing, and biomedical engineering<sup>[47]</sup>; its primary applications lie in rehabilitation—especially motor and speech recovery, and virtual reality control, which accounts for nearly half of the current research—using paradigms like P300, SSVEP, and motor imagery to improve life quality in patients with neurological impairments, while studies show that BCI learning not only modulates motor cortex activity but also induces plastic changes in resting-state networks<sup>[48]</sup>; however, BCI performance is shaped by external factors (e.g., system type, training protocol, feedback design, EEG stability<sup>[49]</sup>) and internal factors (e.g., attention, motivation, emotion<sup>[50]</sup>), and despite promising lab results, practical use remains constrained by issues such as signal interference and system robustness<sup>[49]</sup>, highlighting the future need to enhance non-invasive EEG resolution and integrate artificial intelligence and ethical safeguards for real-world deployment.

## **4. Applications and Clinical Studies of Electronic Implantation and Neural Regeneration**

Electrode implantation and nerve regeneration are important intersections in the fields of neuroscience and biomedical engineering, aiming to repair damage to the central nervous system (CNS) and peripheral nervous system (PNS) through innovative technologies, especially for traumatic brain injury, spinal cord injury, and peripheral nerve injury. The following review integrates the provided abstract content and combines my analysis to discuss the application and current clinical research status and future directions of this topic.

### **4.1 Regenerative strategies for central nervous system injury**

Central nervous system injury (such as brain and spinal cord trauma) leads to severe tissue degeneration and functional loss. The review summarizes the epidemiology and pathogenesis of traumatic injury, emphasizing the challenges of promoting regeneration and limiting degeneration<sup>[51]</sup>. Treatment strategies include drug delivery, cell-based therapies, and tissue engineering methods, aiming to achieve functional recovery. For example, drug delivery may improve the neural environment by controlling the release of neuroprotective factors or inhibiting inflammatory responses; cell therapy such as transplanting adult neural stem cells has been proven to integrate into host tissues and promote neuronal survival in animal models<sup>[52]</sup>. Additionally, tissue engineering methods provide physical and chemical support for axon regeneration by constructing supportive scaffolds.

Repairing spinal cord injury is particularly complex due to inhibitory factors in the body, such as scar tissue and myelin-related inhibitory molecules, which hinder axon regeneration<sup>[53]</sup>. Currently, there is no complete solution for curing spinal cord injury. The research focuses on creating an environment conducive to regeneration, such as providing supportive matrices with biomaterials or using immune molecules to regulate synaptic plasticity<sup>[52]</sup>. Future directions may include exploring the regeneration mechanisms of peripheral nerves (such as the biochemical characteristics of Schwann cells) for application in CNS repair, providing new ideas for spinal cord injury, multiple sclerosis, and neurodegenerative diseases (such as Parkinson's disease)<sup>[54]</sup>.

### **4.2 Biological engineering strategies for peripheral nerve repair**

Peripheral nerve injury is common in trauma or surgical complications. Mild injuries often recover spontaneously, but severe injuries (such as nerve defects of several centimeters) often require surgical intervention. Traditional methods rely on autologous nerve grafts, but are limited by the availability of donor nerves and the complications of additional surgeries. The review emphasizes the necessity of developing tissue-engineered nerve grafts that match or exceed the performance of autologous grafts while reducing complications at the donor site<sup>[55]</sup>.

Biological engineering strategies also include the use of conductive and electroactive materials, such as graphene derivatives, fullerenes, and conjugated polymers (such as polypyrrole, polystyrene), which have been widely studied since the 1970s<sup>[56]</sup>. These materials have comparable electrical

properties to metals and can be modified with biomolecules to obtain biomimetic mechanical and chemical properties. Conductive materials are considered to enhance neural signal transmission and axon regeneration in peripheral nerves, spinal cords, brains, eyes, and ears, showing potential in *in vivo* research and clinical trials<sup>[56]</sup>. For example, recent studies have explored the development of biodegradable conductive materials, which may significantly impact the field of tissue regeneration in the future.

Furthermore, current surgical decisions face challenges, such as the lack of non-invasive techniques to assess the degree of nerve injury and track axon regeneration, resulting in poor surgical outcomes after "delayed" repair<sup>[55]</sup>. The review points out that the degeneration of distal nerve support structures and target tissues further hinders functional recovery, so developing methods to maintain the efficacy of the regeneration process (such as protecting the distal pathways) is crucial.

### 4.3 Clinical research and emerging technologies

Clinical research further reveals the diverse strategies for nerve repair. For instance, the 200th anniversary symposium of Karolinska Institute discussed research on neural regeneration from the molecular level to clinical methods, including the promotion of neuronal survival by transplanting neural stem cells, the role of vascularization in spinal nerve root replantation, and the use of microarray technology for mapping neural regeneration biological patterns. Additionally, novel repair strategies such as using ethyl cyanoacrylate adhesives to repair peripheral nerve injuries have shown comparable functional recovery to traditional nerve suturing, demonstrating the potential of alternative methods<sup>[52]</sup>.

In the field of pain management, studies have demonstrated the significant effect of mirror therapy in treating phantom limb pain after amputation, suggesting a potential link between neural regeneration and pain regulation<sup>[52]</sup>. Moreover, surgical techniques such as repairing avulsed spinal nerve roots have shown potential for restoring motor and sensory functions in clinical practice, but their long-term effects and applicability still need to be verified.

### 4.4 Challenges and Future Prospects

Despite the significant progress made, the field of electronic implants and neural regeneration still faces multiple challenges. Firstly, the long-term biocompatibility and safety of conductive materials need to be further verified, especially in CNS applications. Secondly, the economic cost and feasibility of clinical translation are bottlenecks for widespread application. Additionally, the differences in repair capabilities between peripheral nerves and central nerves (such as the key role of Schwann cells in PNS regeneration) have not yet been fully unlocked, providing research space for using peripheral nerve elements to repair CNS<sup>[54]</sup>.

My analysis suggests that future research should focus on multidisciplinary integration, such as combining electronic implants (e.g., conductive materials) and regeneration strategies to develop intelligent neural interfaces for real-time monitoring and regulation of neural activity. At the same time, it is necessary to strengthen clinical trial design to ensure the safety and effectiveness of new technologies. For example, developing non-invasive imaging techniques to assess the process of nerve injury and regeneration, or exploring the clinical application of biodegradable conductive materials, may significantly promote the development of this field.

Electrode implantation and nerve regeneration have shown great potential in the repair of CNS and PNS injuries, covering drug delivery, cell therapy, tissue engineering and the application of conductive materials. Progress has been made in peripheral nerve repair, but complete repair of spinal cord injuries still requires breakthroughs. In the future, by combining the regeneration mechanisms of peripheral nerves and emerging conductive materials, new therapies for CNS diseases may be provided. I believe that solving the issues of material biocompatibility, clinical conversion costs and long-term effect assessment will be key to achieving seamless transition from basic research to clinical application.

## 5. Challenges and Ethical Issues

Electrode implantation and neural regeneration technologies aim to restore neural function in hard-to-treat conditions but face technical and ethical challenges. Technically, issues include poor biocompatibility, immune responses, and inflammation—requiring natural materials and better mechanical matching<sup>[57]</sup>; long-term stability and electrochemical performance are also critical, as miniaturization increases impedance and reduces charge capacity, while uneven electric fields cause signal “crosstalk”<sup>[58, 59]</sup>; electrode design must ensure selective targeting without harming nearby tissue<sup>[60]</sup>. For example, e-dura, a soft, durable film by Minev et al., addresses mechanical mismatch<sup>[61]</sup>. Ethically, risks such as surgical complications, device failure, stimulation side effects, and privacy concerns demand thorough evaluation and clear informed consent<sup>[59]</sup>; clinically, devices like deep brain stimulators may affect autonomy and identity, requiring fair screening and access to uphold social justice<sup>[62]</sup>. Future work should focus on biocompatible, flexible materials<sup>[57]</sup>, improved electrode designs using advanced nanomaterials, enhanced stimulation precision via optoelectronics<sup>[60]</sup>, robust consent protocols<sup>[59]</sup>, equitable access<sup>[62]</sup>, and interdisciplinary collaboration for responsible translation.

## 6. Future development direction

### 6.1 The current research status

Current research aims to develop low-power, minimally invasive long-term implantable devices to reduce patient burden and address mechanical mismatch between rigid electronics and soft tissue<sup>[63]</sup>; utilize soft, stretchable electronic systems and self-powered personalized devices via energy harvesting to monitor biomechanical and biochemical signals and treat chronic diseases<sup>[64]</sup>; advance electrical stimulation therapies despite limitations in duration and infection risk; employ bioelectronic catheters with conductive materials and 3D manufacturing for repairing critical nerve defects<sup>[65]</sup>; explore silicon nanowire technologies for nerve–electronic interfacing and neural computer interfaces; and promote interdisciplinary integration of neural regeneration and prosthesis—emphasizing electric-field–driven axonal growth, synthetic-biological hybrid interfaces, patterned neural activities in rehabilitation, and enhanced collaboration and flexible funding mechanisms<sup>[66]</sup>.

Table 2. Summarizes the current research and the related challenges.

Research field	Key progress	The main challenge
Material development	Soft, stretchable and biocompatible materials	Long-term stability and foreign body reaction[63, 64]
Equipment design	Self-powered, miniaturized, biodegradable devices	Low-power consumption and minimally invasive implantation technology
Application of electrical stimulation	Promote tissue regeneration (such as nerve and bone)	Clinical application time limit and infection risk[65]
Domain integration	The combination of nerve regeneration and neural prostheses	Interdisciplinary cooperation and funding mechanism[66]
Interface technology	Silicon nanowire interface	The stability and safety of long-term in vivo use

### 6.2 Future directions and personal opinions

Future research should develop stable, biocompatible, highly conductive flexible electronics via surface modification to reduce scarring<sup>[63]</sup>; investigate silicon nanowires for neural interfaces; create low-power or self-powered, miniaturized, biodegradable implants with integrated sensing and feedback for dynamic electrical stimulation adjustment<sup>[64, 65]</sup>; optimize stage-specific stimulation

protocols and study their in vivo, in vitro, and clinical mechanisms—especially patterned neural activity; advance to clinical trials with safety, ethical, and data-privacy safeguards while standardizing processes to accelerate industrialization; and foster interdisciplinary collaboration among neuroscientists, engineers, materials scientists, and clinicians, leveraging flexible funding and personalized treatments to overcome material stability and translation challenges<sup>[65, 66]</sup>.

## References

- [1] DAESCHLER S C, FEINBERG K, HARHAUS L, et al. Advancing Nerve Regeneration: Translational Perspectives of Tacrolimus (FK506) [J]. *Int J Mol Sci*, 2023, 24(16).
- [2] O'BRIEN A L, WEST J M, SAFFARI T M, et al. Promoting Nerve Regeneration: Electrical Stimulation, Gene Therapy, and Beyond [J]. *Physiology (Bethesda)*, 2022, 37(6): 0.
- [3] KUBIAK C A, GROCHMAL J, KUNG T A, et al. Stem-cell-based therapies to enhance peripheral nerve regeneration [J]. *Muscle Nerve*, 2020, 61(4): 449-59.
- [4] WU W, ZHANG J, CHEN Y, et al. Genes in Axonal Regeneration [J]. *Mol Neurobiol*, 2024, 61(10): 7431-47.
- [5] COSTA A R, SOUSA M M. Non-Muscle Myosin II in Axonal Cell Biology: From the Growth Cone to the Axon Initial Segment [J]. *Cells*, 2020, 9(9).
- [6] OLSON L. NGF and the treatment of Alzheimer's disease [J]. *Exp Neurol*, 1993, 124(1): 5-15.
- [7] COLUCCI-D'AMATO L, SPERANZA L, VOLPICELLI F. Neurotrophic Factor BDNF, Physiological Functions and Therapeutic Potential in Depression, Neurodegeneration and Brain Cancer [J]. *Int J Mol Sci*, 2020, 21(20).
- [8] UYEDA A, MURAMATSU R. Molecular Mechanisms of Central Nervous System Axonal Regeneration and Remyelination: A Review [J]. *Int J Mol Sci*, 2020, 21(21).
- [9] SUNDARAM V K, SCHÜTZ V, SCHRÖTER N H, et al. Adipo-glial signaling mediates metabolic adaptation in peripheral nerve regeneration [J]. *Cell Metab*, 2023, 35(12): 2136-52.e9.
- [10] JESSEN K R, MIRSKY R, LLOYD A C. Schwann Cells: Development and Role in Nerve Repair [J]. *Cold Spring Harb Perspect Biol*, 2015, 7(7): a020487.
- [11] MOLINA-GONZALEZ I, HOLLOWAY R K, JIWAJI Z, et al. Astrocyte-oligodendrocyte interaction regulates central nervous system regeneration [J]. *Nat Commun*, 2023, 14(1): 3372.
- [12] CHELYSHEV Y A, KABDESH I M, MUKHAMEDSHINA Y O. Extracellular Matrix in Neural Plasticity and Regeneration [J]. *Cell Mol Neurobiol*, 2022, 42(3): 647-64.
- [13] HOPKINS J M, FORD-HOLEVINSKI T S, MCCOY J P, et al. Laminin and optic nerve regeneration in the goldfish [J]. *J Neurosci*, 1985, 5(11): 3030-8.
- [14] LUKOMSKA A, RHEAUME B A, FROST M P, et al. Augmenting fibronectin levels in injured adult CNS promotes axon regeneration in vivo [J]. *Exp Neurol*, 2024, 379: 114877.
- [15] DE GROEF L, VAN HOVE I, DEKEYSTER E, et al. MMPs in the neuroretina and optic nerve: modulators of glaucoma pathogenesis and repair? [J]. *Invest Ophthalmol Vis Sci*, 2014, 55(3): 1953-64.
- [16] LI T, JAVED R, AO Q. Xenogeneic Decellularized Extracellular Matrix-based Biomaterials For Peripheral Nerve Repair and Regeneration [J]. *Curr Neuropharmacol*, 2021, 19(12): 2152-63.
- [17] ZUPANC G K H, MONAGHAN J R, STOCUM D L. Adult Neural Stem Cells in Development, Regeneration, and Aging [J]. *Dev Neurobiol*, 2019, 79(5): 391-5.
- [18] ZHAO X, MOORE D L. Neural stem cells: developmental mechanisms and disease modeling [J]. *Cell Tissue Res*, 2018, 371(1): 1-6.
- [19] YANG L, LIU S C, LIU Y Y, et al. Therapeutic role of neural stem cells in neurological diseases [J]. *Front Bioeng Biotechnol*, 2024, 12: 1329712.
- [20] GUO W, ZHANG X, ZHAI J, et al. The roles and applications of neural stem cells in spinal cord injury repair [J]. *Front Bioeng Biotechnol*, 2022, 10: 966866.
- [21] OZ T, KAUSHIK A, KUJAWSKA M. Neural stem cells for Parkinson's disease management: Challenges, nanobased support, and prospects [J]. *World J Stem Cells*, 2023, 15(7): 687-700.

- [22] GOUTMAN S A, SAVELIEFF M G, SAKOWSKI S A, et al. Stem cell treatments for amyotrophic lateral sclerosis: a critical overview of early phase trials [J]. *Expert Opin Investig Drugs*, 2019, 28(6): 525-43.
- [23] LEE-KUBLI C A, LU P. Induced pluripotent stem cell-derived neural stem cell therapies for spinal cord injury [J]. *Neural Regen Res*, 2015, 10(1): 10-6.
- [24] GAO J, LIAO Y, QIU M, et al. Wnt/ $\beta$ -Catenin Signaling in Neural Stem Cell Homeostasis and Neurological Diseases [J]. *Neuroscientist*, 2021, 27(1): 58-72.
- [25] XIE J, JIN B, LI D W, et al. Effect of laminin-binding BDNF on induction of recurrent laryngeal nerve regeneration by miR-222 activation of mTOR signal pathway [J]. *Am J Transl Res*, 2015, 7(6): 1071-80.
- [26] ALTMANN C, VASIC V, HARDT S, et al. Progranulin promotes peripheral nerve regeneration and reinnervation: role of notch signaling [J]. *Mol Neurodegener*, 2016, 11(1): 69.
- [27] PARK S, KOPPEL R A, FRORIEP U P, et al. Optogenetic control of nerve growth [J]. *Sci Rep*, 2015, 5: 9669.
- [28] JUCKETT L, SAFFARI T M, ORMSETH B, et al. The Effect of Electrical Stimulation on Nerve Regeneration Following Peripheral Nerve Injury [J]. *Biomolecules*, 2022, 12(12).
- [29] HENDERSON J M, FEDERICI T, BOULIS N. Optogenetic neuromodulation [J]. *Neurosurgery*, 2009, 64(5): 796-804; discussion
- [30] LIL L, LID, WANG Y, et al. Implantable Zinc-Oxygen Battery for In Situ Electrical Stimulation-Promoted Neural Regeneration [J]. *Adv Mater*, 2023, 35(32): e2302997.
- [31] LEE S, S M S, CABALLERO AGUILAR L M, et al. Biodegradable bioelectronics for biomedical applications [J]. *J Mater Chem B*, 2022, 10(42): 8575-95.
- [32] LEE M, SHIM H J, CHOI C, et al. Soft High-Resolution Neural Interfacing Probes: Materials and Design Approaches [J]. *Nano Lett*, 2019, 19(5): 2741-9.
- [33] CHIANG C H, WANG C, BARTH K, et al. Flexible, high-resolution thin-film electrodes for human and animal neural research [J]. *J Neural Eng*, 2021, 18(4).
- [34] SALEH M S, RITCHIE S M, NICHOLAS M A, et al. CMU Array: A 3D nanoprinted, fully customizable high-density microelectrode array platform [J]. *Sci Adv*, 2022, 8(40): eabj4853.
- [35] SHIMBA K, ASAHINA T, SAKAI K, et al. Recording Saltatory Conduction Along Sensory Axons Using a High-Density Microelectrode Array [J]. *Front Neurosci*, 2022, 16: 854637.
- [36] NELSON B D, KARIPOTT S S, WANG Y, et al. Wireless Technologies for Implantable Devices [J]. *Sensors (Basel)*, 2020, 20(16).
- [37] KHAN S R, PAVULURI S K, CUMMINS G, et al. Wireless Power Transfer Techniques for Implantable Medical Devices: A Review [J]. *Sensors (Basel)*, 2020, 20(12).
- [38] DAS K K, BASU B, MAITI P, et al. Piezoelectric nanogenerators for self-powered wearable and implantable bioelectronic devices [J]. *Acta Biomater*, 2023, 171: 85-113.
- [39] TANG F, YAN F, ZHONG Y, et al. Optogenetic Brain-Computer Interfaces [J]. *Bioengineering (Basel)*, 2024, 11(8).
- [40] PASHAIE R, ANIKEEVA P, LEE J H, et al. Optogenetic brain interfaces [J]. *IEEE Rev Biomed Eng*, 2014, 7: 3-30.
- [41] PASHAIE R, BAUMGARTNER R, RICHNER T J, et al. Closed-Loop Optogenetic Brain Interface [J]. *IEEE Trans Biomed Eng*, 2015, 62(10): 2327-37.
- [42] ISERI E, KUZUM D. Implantable optoelectronic probes for in vivo optogenetics [J]. *J Neural Eng*, 2017, 14(3): 031001.
- [43] CHO M, HAN J K, SUH J, et al. Fully bioresorbable hybrid opto-electronic neural implant system for simultaneous electrophysiological recording and optogenetic stimulation [J]. *Nat Commun*, 2024, 15(1): 2000.
- [44] KAMPASI K, LADNER I, ZHOU J, et al. POEMS (POLYMERIC OPTO-ELECTRO-MECHANICAL SYSTEMS) FOR ADVANCED NEURAL INTERFACES [J]. *Mater Lett*, 2021, 285.
- [45] SCHALK G, MCFARLAND D J, HINTERBERGER T, et al. BCI2000: a general-purpose brain-computer interface (BCI) system [J]. *IEEE Trans Biomed Eng*, 2004, 51(6): 1034-43.

- [46] BAMDAD M, ZARSHENAS H, AUAIS M A. Application of BCI systems in neurorehabilitation: a scoping review [J]. *Disabil Rehabil Assist Technol*, 2015, 10(5): 355-64.
- [47] MRIDHA M F, DAS S C, KABIR M M, et al. Brain-Computer Interface: Advancement and Challenges [J]. *Sensors (Basel)*, 2021, 21(17).
- [48] CASIMO K, WEAVER K E, WANDER J, et al. BCI Use and Its Relation to Adaptation in Cortical Networks [J]. *IEEE Trans Neural Syst Rehabil Eng*, 2017, 25(10): 1697-704.
- [49] HOROWITZ A J, GUGER C, KOROSTENSKAJA M. What External Variables Affect Sensorimotor Rhythm Brain-Computer Interface (SMR-BCI) Performance? [J]. *HCA Healthc J Med*, 2021, 2(3): 143-62.
- [50] HOROWITZ A J, GUGER C, KOROSTENSKAJA M. What Internal Variables Affect Sensorimotor Rhythm Brain-Computer Interface (SMR-BCI) Performance? [J]. *HCA Healthc J Med*, 2021, 2(3): 163-79.
- [51] SHOICHET M S, TATE C C, BAUMANN M D, et al. *Frontiers in Neuroengineering*
- [52] *Strategies for Regeneration and Repair in the Injured Central Nervous System [M]*//REICHERT W M. *Indwelling Neural Implants: Strategies for Contending with the In Vivo Environment*. Boca Raton (FL); CRC Press/Taylor & Francis
- [53] Copyright © 2008, Taylor & Francis Group, LLC. 2008.
- [54] SKÖLD M K, SVENSSON M, TSAO J, et al. Karolinska institutet 200-year anniversary. Symposium on traumatic injuries in the nervous system: injuries to the spinal cord and peripheral nervous system - injuries and repair, pain problems, lesions to brachial plexus [J]. *Front Neurol*, 2011, 2: 29.
- [55] SCHMIDT C E, LEACH J B. Neural tissue engineering: strategies for repair and regeneration [J]. *Annu Rev Biomed Eng*, 2003, 5: 293-347.
- [56] EL SEBLANI N, WELLEFORD A S, QUINTERO J E, et al. Invited review: Utilizing peripheral nerve regenerative elements to repair damage in the CNS [J]. *J Neurosci Methods*, 2020, 335: 108623.
- [57] PFISTER B J, GORDON T, LOVERDE J R, et al. Biomedical engineering strategies for peripheral nerve repair: surgical applications, state of the art, and future challenges [J]. *Crit Rev Biomed Eng*, 2011, 39(2): 81-124.
- [58] MANOUSIOUTHAKIS E, PARK J, HARDY J G, et al. Towards the translation of electroconductive organic materials for regeneration of neural tissues [J]. *Acta Biomater*, 2022, 139: 22-42.
- [59] REDOLFI RIVA E, MICERA S. Progress and challenges of implantable neural interfaces based on nature-derived materials [J]. *Bioelectron Med*, 2021, 7(1): 6.
- [60] STIEGLITZ T. Considerations on surface and structural biocompatibility as prerequisite for long-term stability of neural prostheses [J]. *J Nanosci Nanotechnol*, 2004, 4(5): 496-503.
- [61] HENDRIKS S, GRADY C, RAMOS K M, et al. Ethical Challenges of Risk, Informed Consent, and Posttrial Responsibilities in Human Research With Neural Devices: A Review [J]. *JAMA Neurol*, 2019, 76(12): 1506-14.
- [62] GRILL W M, NORMAN S E, BELLAMKONDA R V. Implanted neural interfaces: biochallenges and engineered solutions [J]. *Annu Rev Biomed Eng*, 2009, 11: 1-24.
- [63] MINEV I R, MUSIENKO P, HIRSCH A, et al. Biomaterials. Electronic dura mater for long-term multimodal neural interfaces [J]. *Science*, 2015, 347(6218): 159-63.
- [64] GLANNON W. Ethical issues in neuroprosthetics [J]. *J Neural Eng*, 2016, 13(2): 021002.
- [65] RENZ A F, REICHMUTH A M, STAUFFER F, et al. A guide towards long-term functional electrodes interfacing neuronal tissue [J]. *J Neural Eng*, 2018, 15(6): 061001.
- [66] SONG Y, MIN J, GAO W. Wearable and Implantable Electronics: Moving toward Precision Therapy [J]. *ACS Nano*, 2019, 13(11): 12280-6.
- [67] MAENG W Y, TSENG W L, LI S, et al. Electroceuticals for peripheral nerve regeneration [J]. *Biofabrication*, 2022, 14(4).
- [68] GRILL W M, MCDONALD J W, PECKHAM P H, et al. At the interface: convergence of neural regeneration and neural prostheses for restoration of function [J]. *J Rehabil Res Dev*, 2001, 38(6): 633-9.