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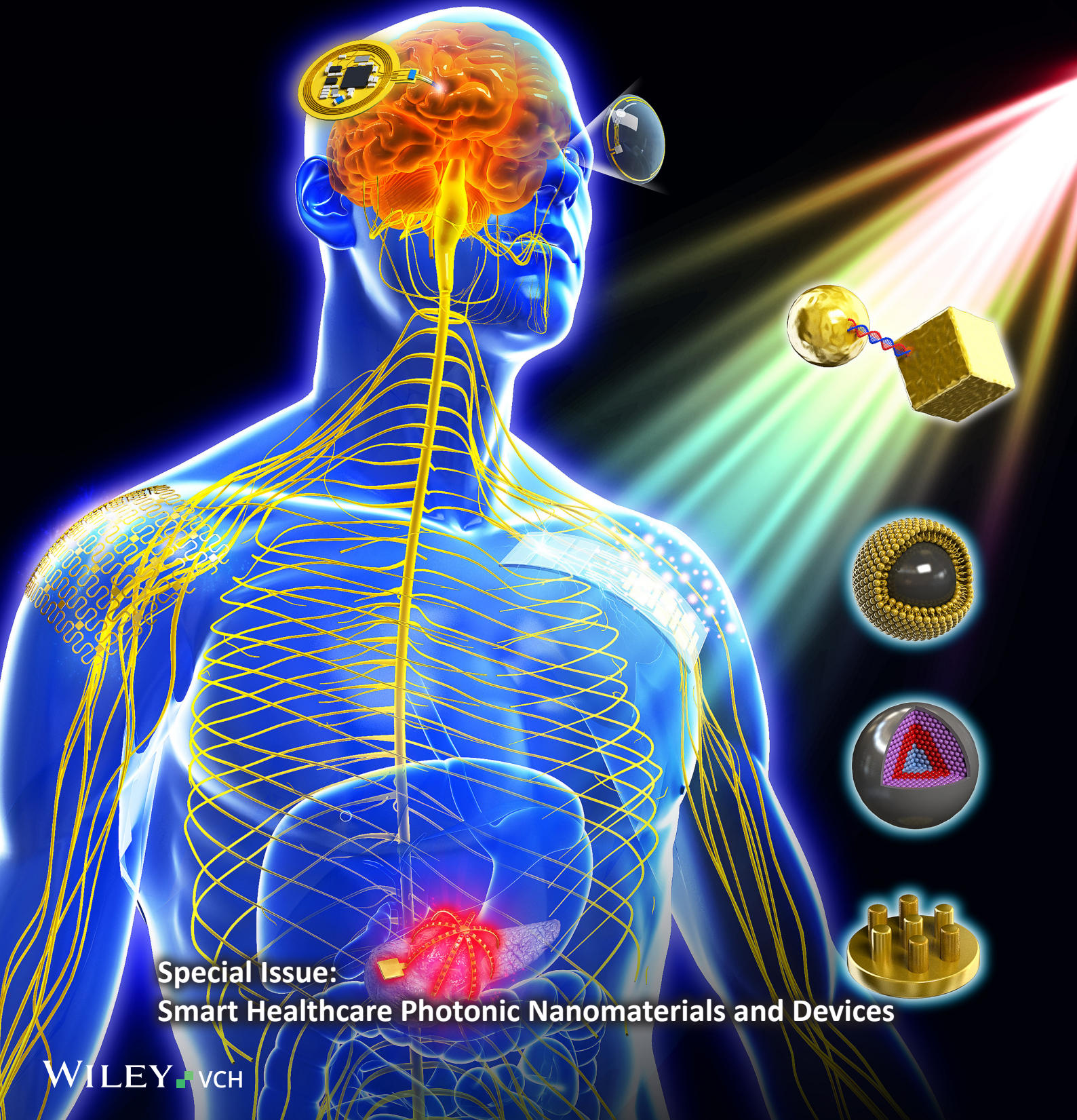

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Multifunctional Photonic Nanomaterials and Devices for Digital Photomedicine via Neuro-Immune Cross-Talks

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The nervous and immune systems are closely interconnected, and influence the onset and progress of various diseases. Accordingly, understanding the interaction of the neural system and the immune system becomes very important for the treatment of intractable diseases with the analysis of therapeutic mechanisms, such as autoimmune diseases, neurodegenerative diseases, cancers, and so on. The conventional immunomodulation treatments have been mainly carried out by drug administration, but they have suffered from systemic negative side-effects with only limited effects on the specific disease. In this Perspective, photonic nanomaterials and devices are reviewed and discussed for digitally controlled neurostimulating photomedicine via photobiomodulation and optogenetics from the unique viewpoint of neuro-immune cross-talks. The prospects and perspectives to integrate photonic nanomaterials with advanced wearable and implantable healthcare devices are also provided and highlighted to revolutionize the therapeutic strategies by the interaction of neural and immune systems, and optimize the treatment protocols for futuristic digital photomedicine. This approach will revolutionize the fields of neurostimulation and immune regulation for further clinical applications.

1. Introduction

In modern medicine, regulating the immune system is crucial for treating autoimmune disorders, inflammatory diseases, infections, and cancers.[1–4] Traditional pharmacological approaches often suffer from systemic side effects with variable efficacy. Neuromodulation, which involves influencing neuronal activity through electrical, magnetic, photonic, and/or pharmacological means, presents a promising protocol for precisely targeting immune functions.[5,6] This is primarily mediated by the autonomic nervous system, with a particular emphasis on the vagus nerve (VN), which has been shown to regulate inflammatory processes via the cholinergic anti-inflammatory pathway.[7,8] Techniques such as VN stimulation are being explored for their therapeutic potential in reducing autoimmune and inflammatory responses.[8,9] The intricate relationship between the nervous and immune systems is a rapidly expanding area of research, offering the potential of neurostimulation near critical physiological barriers, such as the brain,[6] lung,[10] and gut,[11] to influence immune functions (**Figure 1**). This approach leverages the close anatomical and functional connections between these barriers and the nervous systems to regulate immune activity in a targeted and precise manner. For example, neuromodulation allows for the precise control of meningeal sensory nerves in the brain to adjust macrophage activity for protection from bacterial invasion.[12] The activation of sensory nerves in the skin via optical methods can accelerate wound healing by orchestrating the responses of neutrophils and macrophages.[13] Similarly, the modulation of VN in the gastrointestinal tract can alleviate the severity of inflammatory bowel diseases, such as Crohn's disease, by adjusting cytokine levels and immune cell activity.[11,14]

Photobiomodulation, the therapeutic use of light to stimulate cellular function and enhance physiological processes, is emerging as a facile promising technique in neuroscience. Particularly, the use of red to infrared light (from 600 to 1060 nm) has shown considerable potential in targeting brain regions to modulate neurological activity.[15–17] This non-invasive approach capitalizes on the ability of red light to penetrate biological tissues

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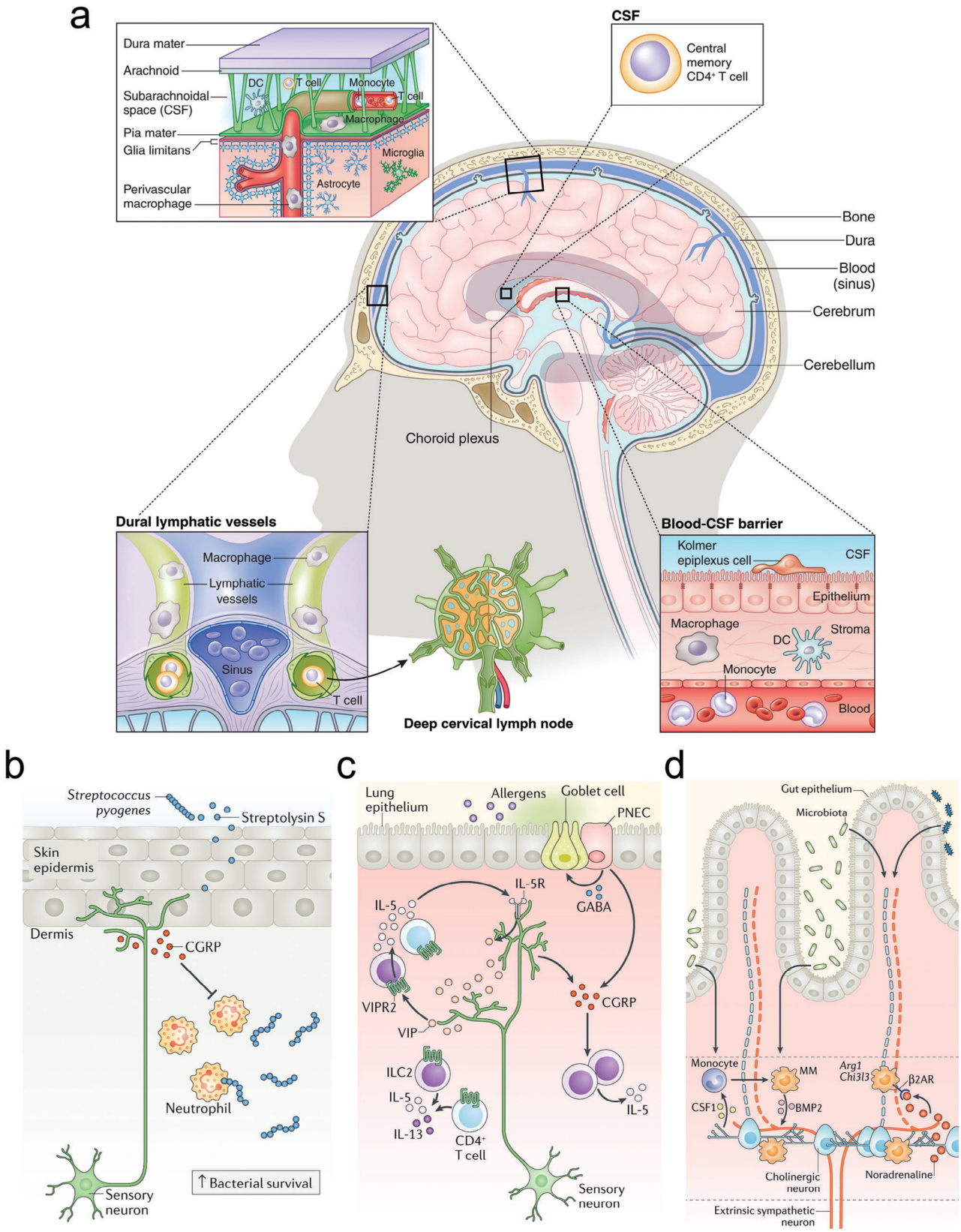


Figure 1. Neuro-immune cross-talks at barrier surfaces. Neuroimmunological barriers in a) brain, Reproduced with permission,[1] Copyright 2017, Springer Nature, b) skin c) lung, and d) intestine. Reproduced with permission,[2] Copyright 2019, Springer Nature.

and influence cellular and neurological functions. Photobiomodulation is based on activating photoreceptors in cells, leading to a cascade of biological effects. When applied to neurological tissues, red light can enhance mitochondrial function, increasing adenosine triphosphate (ATP) production and improving cellular energy metabolism.[18,19] This enhancement supports neuroprotection, promotes neurogenesis, and can modulate neurotransmitter release, thereby effectively influencing neurological circuits and brain function.[20] Recent studies have employed red light-emitting diodes (LEDs) to deliver precise light doses to specific brain regions through the skull, aiming to stimulate or inhibit neurological activity.[16,20,21] This technique offers a targeted method to modulate neurological pathways, providing potential therapeutic benefits for a range of neurological and psychiatric conditions, including depression,[22] anxiety,[23] brain injury,[16] and neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.[24] In addition, photobiomodulation shows great potential to affect immune responses and reduce inflammation through several key mechanisms. One notable approach in photobiomodulation is the control of macrophage polarization for anti-inflammation and tissue healing.[25–29] As reported elsewhere,[30,31] this kind of photobiomodulation could reduce neuroinflammation and attenuate amyloid-β plaques to improve cognitive function in Alzheimer's disease models. The dual function of photobiomodulation for neuronal excitation and anti-inflammation provides a compelling link between phototherapy and immunotherapy.

Optogenetics is a revolutionary technique that combines genetics and optics to control and monitor the activities of individual neurons in living tissues with high precision.[32] This innovative approach uses light-sensitive proteins, known as opsins, which are introduced into specific neurons via genetic engineering.[33] By illuminating these neurons with the light of particular wavelengths (470, 580, and 620 nm), researchers can precisely control their activity, either activating or inhibiting them in real time. The power of optogenetics lies in its ability to provide temporal and spatial precision that surpasses traditional methods such as electrical stimulation.[34–36] This precision enables scientists to dissect the complex neurological circuits underlying behaviors, cognition, and neurological disorders.[6,37,38] For instance, optogenetics has been instrumental in identifying the neurological circuits involved in movement, addiction, and various psychiatric disorders, providing meaningful insights that were previously unattainable. In addition, recent research has shown that neurons play a critical role in regulating both innate and adaptive immune responses. Notably, activating sensory neurons has resulted in the inhibition of immune responses to facilitate wound healing, whereas suppressing sensory neurons has enhanced immune responses in cancer immunotherapy.[13,39] Clinically, there is great potential for developing optogenetic-based therapies to treat neurological and psychiatric disorders by selectively targeting dysfunctional neurological circuits.[40] Although multifunctional photonic nanomaterials and devices have been developed for neurostimulation, there is still a notable lack of research on using these materials and devices to stimulate nerves for immune regulation.[41–43] Accordingly, the development of wearable and implantable photonic nanomaterials and devices is crucial for advancing neurostimulation techniques near the brain, lung, gut barriers. These materials and devices enable precise control and delivery of light near the barriers, facilitating targeted modulation of neurological and immune responses. By enhancing the efficacy and specificity of photonic neurostimulation, these innovations can lead to more effective treatments for a variety of neuro-immune-related disorders.

These photonic materials and devices are typically composed of flexible gold electrodes, miniaturized LEDs, and soft polymeric substrates.[44–46] The mechanical flexibility, which matches with that of surrounding tissues, and the miniaturized sizes of the devices facilitate their minimally invasive placement and operation in vivo.[47,48] Despite significant advances in device design and engineering, much less attention has been given to the development and optimization of the bio-interface between target tissues and photo-medical implants. In these types of implants, photonic modules are enclosed within a rigid case to shield them from biological environments and they are linked to metal electrodes through insulated wiring to form interfaces with biological tissue. Although these configurations have been effective for patient treatment globally, they have limitations in scalability, especially for achieving a high number of interface points, and struggle to establish contact over-broad, curved surfaces or within larger volumetric spaces.[49] On the other hand, fundamentally different optoelectronic device designs, such as functional thin-film membranes, flexible filaments, and open network meshes, seem promising for the advanced levels of functional integration.[50,51] Beyond the limitation of conventional rigid devices, these innovative systems hold promise for more sophisticated neurological interfaces to better regulate immune responses, paving new pathways for treating both neurological and immune-related disorders.

In this *Perspective*, we will overview and comment on the innovative neurostimulation methods using photonic nanomaterials and devices for digital photomedicine, in terms of neuro-immune cross-talks. We will discuss the recent development in photobiomodulation and optogenetics, highlighting their potential for advancing therapeutic strategies. Additionally, we will analyze the integration of photonic nanomaterials with advanced wearable and implantable healthcare devices, emphasizing their potential to enhance the understanding of neuro-immune interactions and optimize treatment protocols. Finally, the challenges and prospects of using these technologies to revolutionize treatments for a variety of immune-related disorders will be discussed for further development.

2. Fundamentals of Neuroimmunology

Neuroimmunology is a field that examines the complex and dynamic interplay between the nervous and immune systems. These systems play a pivotal role in tissue homeostasis and host defense in various organs of the body.[3,52,53] Immune cells are monitored and regulated by the nervous system, while neurons and glial cells are under immune surveillance and control.[54] Accordingly, it is critical to understand and leverage neuro-immune cross-talks in order to enhance the treatment and potential cure of a myriad of diseases.

2.1. Neuro-Immune Cross-Talks for Neuroimmunotherapy

2.1.1. Neuro-Immune Cross-Talk Niches

The central nervous system (CNS), comprising the brain, retina, and spinal cord, has historically been considered an immune-privileged site. However, the barriers that surround the CNS, such as the meninges, skull, choroid plexus, and perivascular spaces have been identified as immunological niches where leukocytes, lymphatics, and other tissues and fluids constitute a local brain immune system.[55,56] This paradigm shift has redefined the CNS and immune system as interdependent rather than isolated entities. Furthermore, beyond the CNS, nerves are distributed throughout the body and participate in neuro-immune interactions at specialized barrier sites, like the meninges, skin, lung, and intestines, where neurons and immune cells converge.[3] Recently, it has been reported that a brain stem region and specific neuronal populations respond to immune stimuli.[8,57] Koren et al.[58] has reported that insular cortex neurons in the brain encode and retrieve peripheral immune responses. There has been no report on undesired significant side effects by regulating the central nervous system. Nonetheless, the specific mechanisms by which the central nervous system sends signals back to the immune system to regulate inflammation remain still elusive. Further research is required to unravel the complicated interactions between the central nervous system and the immune system, which will be crucial for targeted therapies.

2.1.2. Neurotransmitters and Cytokines for Neuro-Immune Cross-Talks

Neurotransmitters are signaling molecules that are essential for communication within the nervous system. It is noteworthy that these neurotransmitters significantly impact the immune system as immune cells possess receptors for these neurotransmitters, indicating their broader biological function. Similarly, neurons are equipped with receptors for pathogen-associated molecular patterns (PAMPs) or cytokines, which enable them to monitor the immune status during both homeostasis and inflammation. This bidirectional communication underscores a sophisticated interplay between the nervous and immune systems, suggesting a deeply integrated mechanism that governs bodily responses.[3,52,53]

2.1.3. Neuro-Immune Cross-Talks in Neurological Disorders

Neuro-immune interactions play a pivotal role in the pathogenesis of various brain diseases, including Alzheimer's disease, brain tumors, multiple sclerosis, and psychiatric disorders.[55] In Alzheimer's disease, neuroinflammatory responses contribute to the accumulation of amyloid-beta and the development of tau pathology, which are considered hallmarks of the disease. Microglia, the brain-resident macrophages, dysfunction contribute to Alzheimer's disease not only by their failure to clear the deposits but also through the secretion of pro-inflammatory cytokines that exacerbate neuronal damage.[59] Brain tumors, particularly gliomas, exploit immune system mechanisms to promote tumor growth and evade immune surveillance, complicating treatment strategies. In particular, T cells, a key component of adaptive immunity, have been found to infiltrate tumor sites and interact with neuronal signals, which can either facilitate tumor growth or enhance anti-tumor immune responses.[60] Multiple sclerosis is a chronic autoimmune and inflammatory disease affecting the central nervous system, leading to demyelination and neurodegeneration. T cells and B cells contribute to the autoimmune response against myelin, leading to demyelination, while microglia and macrophages promote inflammation and neuronal damage by secreting neurotoxic molecules.[61] Furthermore, emerging evidence suggests that brain-immune interactions are a significant factor in psychiatric disorders such as autism, depression and schizophrenia.[62,63] These conditions reveal the intricate and often detrimental interactions between the nervous and immune systems.

2.2. Neuroimmunological Barriers in Organs

The barriers of skin, lung, gut, and brain interface with the external or internal environment, and play a pivotal role in distinguishing between benign and harmful stimuli, maintaining homeostasis and integrity in response to environmental fluctuation.[3,52] These sites are densely populated with nerve and immune cells, orchestrating a complex neuro-immune network. The immune system employs both innate and adaptive arms to protect the host. Concurrently, the nervous system engages peripheral nerves to modulate inflammation and mitigate threats.[3,52] The dynamic interplay between the nervous and immune systems represents the sophisticated defense mechanism in the body.

2.2.1. Neuroimmunological Barriers in the Brain

In the brain, immune cells such as macrophages, dendritic cells, T cells, B cells, innate lymphoid cells (ILCs), and natural killer (NK) cells play crucial roles, particularly at barrier sites like the meninges, skull bone marrow, choroid plexus, and perivascular spaces (Figure 1a).[55,56] In addition, within the brain barrier, the dura mater is densely innervated with sensory nerves, whereas the pia mater and choroid plexus contain sympathetic and parasympathetic autonomic nerves.[64] Macrophages are key in clearing cellular debris and pathogens in the brain[65]; notably, meningeal macrophages are modulated by calcitonin gene-related peptide (CGRP), a neuropeptide released by dural sensory nerves under bacterial invasion,[12] and perivascular macrophages are crucial in sustaining barrier integrity by regulating endothelial cell functions.[66] Dendritic cells at these CNS barriers are instrumental in initiating immune responses, serving as conduits between innate and adaptive immunity and influencing the activity of T cells and B cells.[67] T cells traverse the barriers in response to inflammatory cues, potentially exacerbating neuroinflammation or facilitating immune surveillance.[68] Although less characterized within the CNS context, ILCs and NK cells are implicated in maintaining barrier integrity and modulating inflammatory responses through their cytokine output.[69]

These complicated neuro-immune interactions at brain barriers highlight the intricate immune responses within the CNS and their implications for brain health. Recent studies have shown that the neuromodulation of nerves in the brain barriers may impact immune cell behaviors, protecting from bacterial infections[12] and reducing neuroinflammation in conditions such as multiple sclerosis.[63]

2.2.2. Neuroimmunological Barriers in the Skin

The skin is one of the largest organs in the body, and its integrity is essential for maintaining homeostasis and protecting against pathogens (Figure 1b). The nerve fibers that innervate the skin communicate with resident immune cells, including macrophages, mast cells, dendritic cells, and ILCs, thereby coordinating their essential functions in skin health and diseases.[70,71] Skin macrophages are the most numerous immune cells under normal conditions. These cells serve as key sentinels in pathogen detection and tissue damage and are found to secret neurotrophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) to maintain the growth and survival of neurons.[72] Mast cells are commonly associated with type 2 inflammation and IgE-mediated allergic responses. Mast cell activation is triggered by neuropeptides like Substance P released by nerves, which in turn elicit pruritus by activating nerves in atopic dermatitis.[73] Skin dendritic cells, also known as Langerhans cells, are located in the epidermis and serve as sentinels, sample the environment. These cells respond to CGRP, initiating skin inflammation in psoriasis.[74] ILCs are tissue-resident innate immune cells that play a pivotal role in homeostasis, inflammation, and tissue repair. ILCs are regulated by nerves during atopic dermatitis and psoriasis.[70] These neuro-immune interactions are very important in resolving skin inflammation, providing the basis for innovative therapeutic approaches.

2.2.3. Neuroimmunological Barriers in Lung

Figure 1c shows the neuro-immune interactions between nerves and immune cells in the lung. Peripheral nerves in the lung, including the VN and sensory fibers, play a critical role in modulating immune responses and maintaining pulmonary homeostasis.[70,75] These nerves interact closely with immune cells like macrophages, T cells, and innate ILCs, in asthma, chronic obstructive pulmonary disease (COPD), and pulmonary infections. Lung macrophages are essential for the clearance of pathogens and debris and interact with nerves to perform an immunoregulatory role during lung inflammation.[76] Nociceptor sensory neurons suppressed pulmonary $\gamma\delta$ T cell responses in bacterial lung infections.[77] ILCs, particularly type 2 (ILC2), play a significant role in allergic inflammation and asthma. Vagal sensory nerves suppress ILC2 function and airway inflammation.[10] This bidirectional communication is pivotal in the pathophysiology of respiratory diseases, and targeting these interactions presents a promising avenue for developing novel therapeutic strategies to treat lung disorders.

2.2.4. Neuroimmunological Barriers in the Intestine

The gastrointestinal tract is populated by a variety of immune cells and extensively innervated by the peripheral nervous system (Figure 1d). The intricate interactions between these two systems are critical in maintaining gut homeostasis and modulating inflammation. Within the gastrointestinal tract, peripheral nerves, including autonomic and sensory neurons, along with intrinsic enteric nerves, engage in detail with diverse immune cells such as macrophages, T cells, regulatory T cells (T_{reg} cells), and innate ILCs.[78,79] Gut macrophages interact with the enteric nervous system to regulate motility and inflammatory responses, which are crucial during bacterial infection.[80] T_{reg} cells help maintain intestinal homeostasis and protect against inappropriate immune responses to dietary antigens and commensal bacteria. Meanwhile, nociceptor sensory neurons control the activity of T_{reg} cells in the gut.[81] Furthermore, ILCs are involved in the immune response and tissue repair in the gut, with neurons in active cross-talks with both ILC2 and type 3 ILC (ILC3) to maintain gut homeostasis and combat infections.[82,83] Understanding these complex interactions provides new avenues for therapeutic interventions for gastrointestinal diseases.

2.3. Platform technologies for Neuroimmunotherapy

Figure 2a shows neurological disorders associated with α-synuclein, β-aggregates, and plaque accumulation, along with neuron loss and degeneration, blood-brain barrier (BBB) leakage, neuroinflammation, and autoimmune responses. Recent advances in platform technologies for neuroimmunotherapy, including anti-inflammatory drugs, optogenetics, electrical stimulation, and transcranial magnetic stimulation have been pivotal in elucidating the intricate neuro-immune interactions within various tissues (Figure 2b). Especially, the innovative therapeutic strategies are taking advantage of implantable electrical devices to modulate immune responses via targeted neurostimulation. The bioelectronic medicines are based on implantable electrical devices aimed at modulating immune responses via the neural pathways. Specifically, the use of electrical VN stimulation has gained huge attention for its potential to mitigate inflammatory processes.[7,84–86] Electrical stimulation of VN has been reported to control the secretion of pro-inflammatory cytokines by macrophages, as well as to enhance the release of anti-inflammatory cytokines.[8] However, it has several drawbacks, including limited specificity in regulating neural circuits, high power consumption for signal blocking, challenges in achieving bidirectional regulation, and the low stability of electrodes due to electrochemical reactions under physiological conditions. These limitations can reduce the long-term effectiveness of electrical VN stimulation and lead to potential side effects.

In contrast, optical stimulation provides highly specific, programmable, and bidirectional regulation of nerve activity, enabling greater control over neural circuits. Optogenetics can be employed to either activate neurons via channelrhodopsin-2 (ChR2) and ChrimsonR or inhibit them using halorhodopsin (NpHR), providing a highly specific therapeutic tool for targeting particular brain regions or cellular populations. This precise control is especially important for immune regulations

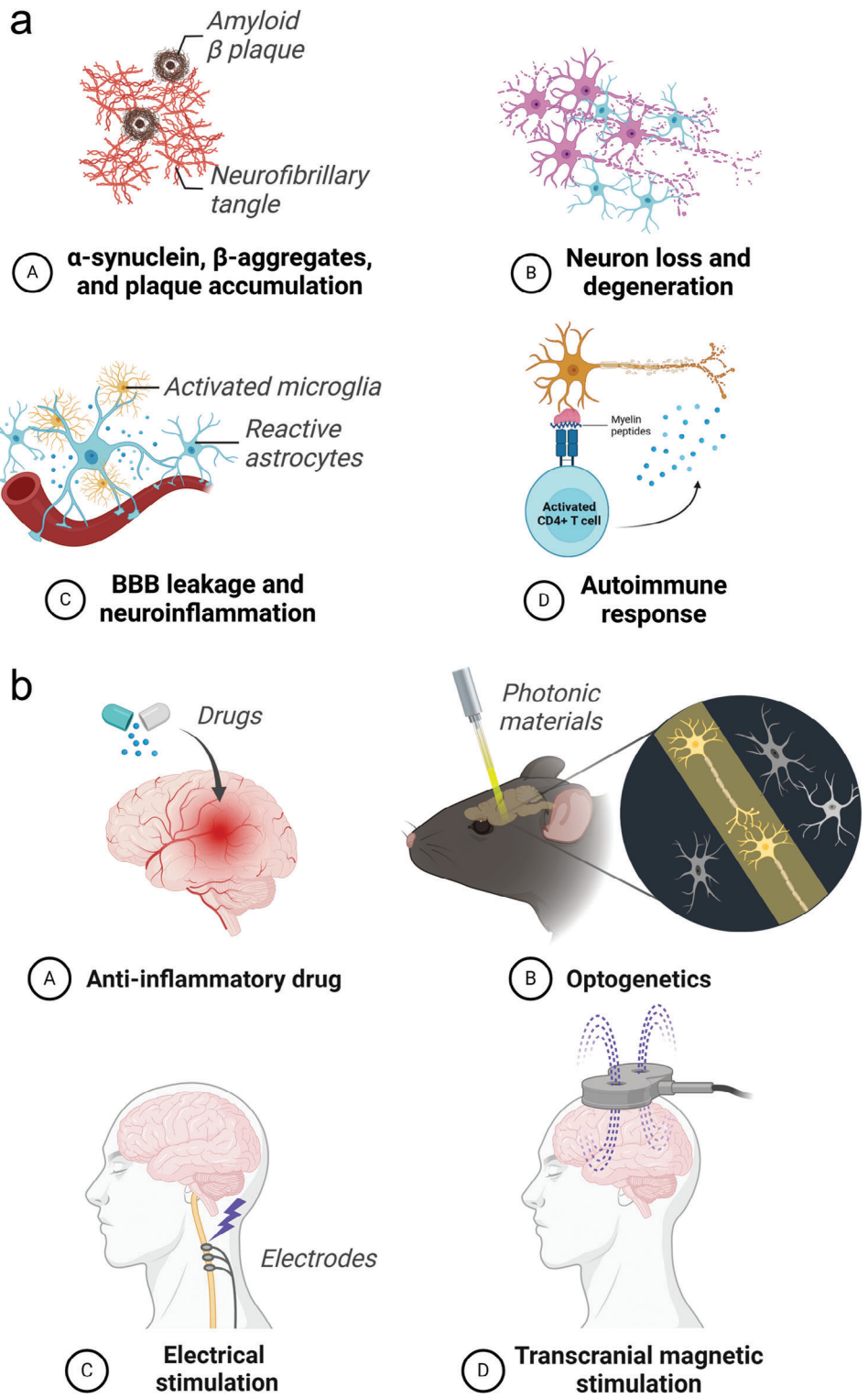


Figure 2. Schematic illustrations for a) neurological disorders and b) platform technologies for neuroimmunotherapy (Created by Biorender.com).

depending on the activation or inhibition of nerves. For instance, optogenetics becomes crucial in such scenarios, as the modulation of sensory neurons can unlock additional therapeutic opportunities, such as treating brain bacterial infections,[12] enhancing anti-tumor immunity by blocking CGRP signaling,[39] or promoting wound healing by activating CGRP signaling.[13] Additionally, it has been reported that both activation and inhibition of peripheral nerves that express opsins such as ChR2 for activation and NpHR for inhibition can potentially regulate immune responses through neuro-immune interactions.[87,88] These findings suggest a critical role for neuro-immune interactions in immune regulation and highlight the increasing demand to engineer devices that exploit this interplay for therapeutic benefits. This emerging field promises to redefine approaches to immune modulation, potentially offering new avenues for treating various inflammatory disorders. While optogenetic-based neurostimulation for immune regulation is underway, there remains a significant gap in exploring neuro-immune cross-talks facilitated by photonic nanomaterials and devices. Accordingly, our aim is to review and discuss photonic nanomaterials and devices for digitally controlled neurostimulation, emphasizing their potential role in facilitating neuro-immune cross-talks.

3. Multifunctional Nanomaterials for Photonic Neuroimmunotherapy

Since the development of cardiac pacemakers in the late 1960s, the electrical neuromodulation of the brain,[89,90] spinal cord,[91] and peripheral nerve[92,93] has drawn great attention to diagnose and treat neurological disorders and associated symptoms. However, the implantation of electrodes into specific neural circuits remains an unsolved challenge for cell-type specific neuromodulation.[94,95] Photobiomodulation and optical neuromodulation have addressed this challenge with advances in photonic materials, fiber optics, and genetics.[96–98] Photobiomodulation leads to various therapeutic effects, including tissue regeneration, pain relief, and anti-inflammatory effects.[18,19,41] Optogenetics can be broadly considered as a kind of photobiomodulation,[41] and optogenetics enables spatiotemporally controlled illumination for targeted activation or inhibition of neuronal activity with opsins genetically expressed in neurons to dissect the neural circuitry that causes specific behaviors and disorders. Despite its desirable advantages, photobiomodulation and optical neuromodulation also faced several critical issues such as the limited penetration depth of light,[99,100] the irradiation-related tissue heating,[101] and the invasiveness of external light sources in neural tissues.[102,103] Up to date, several photonic nanomaterials, including upconversion nanoparticles (UCNPs),[104,105] mechanoluminescent nanoparticles (MLNPs),[106–109] and plasmonic nanoparticles,[110,111] have been developed as a novel tool for photobiomodulation and optogenetics with improved tissue penetration efficiency, precise light transmission to target neurons, and minimal chronic damage to neural tissues.[112] These photonic nanomaterials have potential applications in barrier tissues such as skin, brain barriers, gut, and lung, where external light sources are difficult to reach. Accordingly, photonic nanomaterials are expected to play a key role in advancing neuro-immune regulation by enabling real-time manipulation of neural and immune interactions.

3.1. Upconversion Nanoparticles

UCNPs are photonic nanomaterials doped with lanthanide ions such as Gd, Y, Er, Tm, and Yb, allowing them to absorb near-infrared (NIR) light and up-convert it into visible light (**Figure 3a**).[113–115] These particles consist of a host matrix that forms their crystal structure, with lanthanide cations integrated into the host lattice acting as sensitizers or activators. By adjusting the combination and concentration of host materials, sensitizers, and activators, the emission wavelength of UCNPs can be precisely controlled for biophotonic applications. Compared to conventional photonic materials such as organic dyes or quantum dots, UCNPs offer superior stability, a narrow emission bandwidth, biocompatibility, the capability to deliver visible light to deep tissues using NIR excitation, and a high signal-to-noise ratio (SNR).[116] Their potential is particularly remarkable for biophotonic applications with enhanced upconversion efficiency by modulating the core-shell structures, the development of photomedicine by integrating with other photosensitizers, and improving both upconversion efficiency and biocompatibility by forming a silica shell or multilayer around the UCNP core (Figure 3b–d).[105,117,118]

In the context of UCNP-based optogenetic systems, Shi et al. pioneered the concept of wireless optogenetics using UCNPs, first demonstrating its feasibility in vitro and later achieving wireless brain stimulation in freely moving animals.[119,120] Building on these advancements, McHugh et al. further improved this technology by preparing core-shell structured UCNPs specifically designed for transcranial neuromodulation, enabling the targeted modulation of neural activity in deep brain regions (Figure 3e).[104] As UCNPs can convert NIR light into visible light sufficient to activate opsin-expressing neurons (power density of 0.34 mW mm^{-2}), this less-invasive optogenetic manipulation enables precise control over targeted neurons in the brain. After injecting UCNPs into the ventral tegmental area (VTA) of transgenic mice, they demonstrated the precise localization of UCNPs, NIR-driven activation of ChR2-expressing dopamine neurons, and neuronal activity control of dopamine release by mapping the image of c-Fos (Figure 3f,g). Furthermore, green-emitting UCNPs were able to suppress chemically induced seizures by transcranial NIR inhibition of hippocampal excitatory neurons expressing archaerhodopsin (Arch) in the CA1 and dentate gyrus (DG) regions of the brain. In addition, blue-emitting UCNPs triggered memory recall by stimulating hippocampal engrams expressing ChR2 in the DG regions through transcranial NIR light. They encoded fear memory in active c-fos-expressing DG granule cells labeled with ChR2 and reactivated these cells by NIR stimulation, resulting in the increased freezing behavior in transgenic mice that had both ChR2 expression and UCNP injection under NIR irradiation. However, the system faced some challenges, such as the need for an optical fiber positioned 2 mm above the skull surface to ensure sufficient NIR light transmission (with a power density of 1.4 W mm^{-2} on the skull surface). In addition, the low energy conversion efficiency of UCNPs (~2.5%) and high absorption

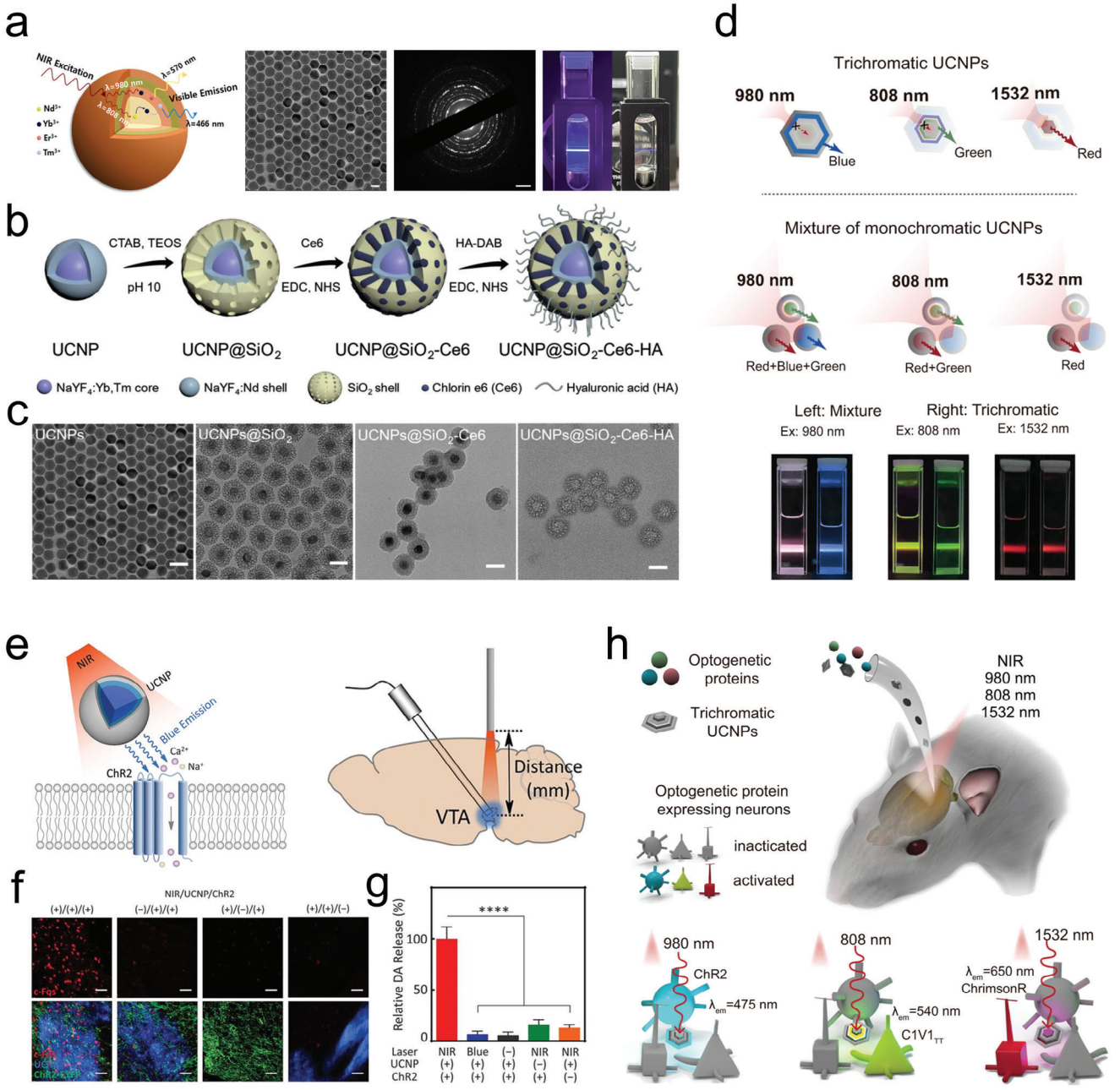


Figure 3. UCNPs for optogenetics. a) Characteristics of UCNPs. Reproduced with permission,[113] Copyright 2022, Elsevier. b) Preparation and c) transmission electron microscopy (TEM) images of silica-shell coated UCNPs. Reproduced with permission,[117] Copyright 2024, John Wiley & Sons. d) Multicolor emission of multilayer UCNPs under different NIR irradiation. Reproduced with permission,[105] Copyright 2021, Springer Nature. e) Optogenetics using silica-shell coated UCNPs for transcranial activation of ChR2. f) Confocal images of c-fos (top) and the overlay (bottom) at VTA after transcranial NIR irradiation under different conditions. All scale bars represent 100 μm. g) Statistical analysis of dopamine release within 15 sec after the start of transcranial activation. Data are presented as mean ± standard error of the mean (SEM), and $^{****}p < 0.0001$. Reproduced with permission,[104] Copyright 2018, American Association for the Advancement of Science. h) Optogenetics using multicolor emission of multilayer UCNPs. NIR light at wavelengths of 980, 808, and 1532 nm penetrates brain tissue, exciting the UCNPs, which then emit visible light at 475, 540, and 650 nm, respectively, activating the corresponding neuronal populations. Reproduced with permission,[105] Copyright 2021, Springer Nature.

of water at 980 nm wavelength necessitated high-intensity NIR light,[99,121] which could potentially induce heating effects in the brain tissue.[101] Although various studies have been conducted to mitigate these limitations, further enhancements in the efficiency of UCNPs are still required to extend the activation depth (Figure 3h).[105,121,122] Moreover, the activation kinetics of ChR2 by the converted blue light were slower than direct blue light activation.[34]

3.2. Mechanoluminescent Nanoparticles

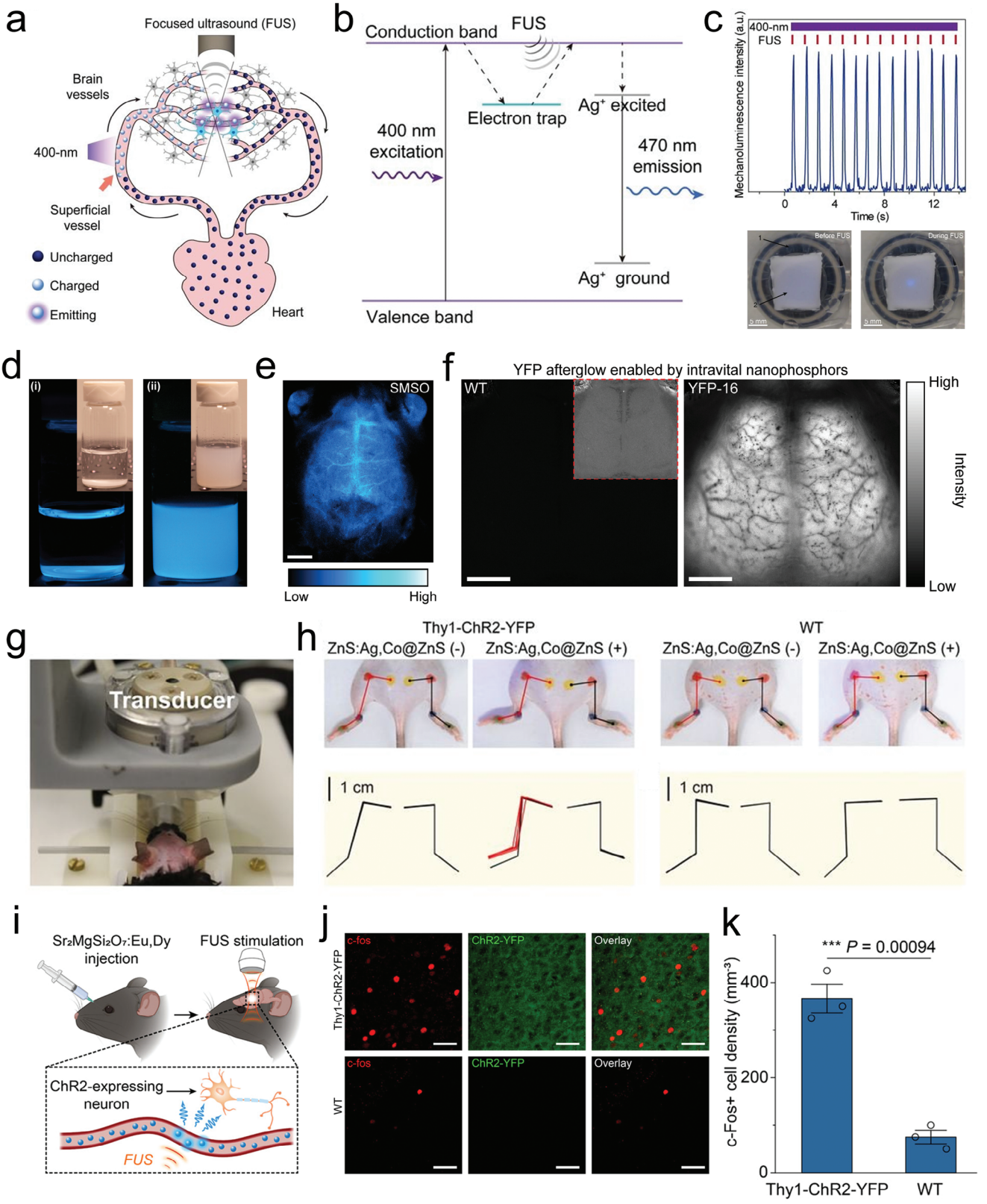
Mechanoluminescence (ML) refers to the emission of light triggered by mechanical forces such as pressure or ultrasound, resulting in high afterglow luminescence (AL) (**Figure 4a**).[106,123–125] In MLNPs, electrons are excited from their ground state to an excited state when irradiated by external light sources (Figure 4b).[106] These excited electrons are then stored in positively charged defect states just below the conduction band. When mechanical stress induces an electric field and charge separation in piezoelectric materials, the stored energy is released as light (Figure 4c). Materials such as ZnS, $Sr_2MgSi_2O_7$, $SrAl_2O_4$, and CaZnOS are commonly used to synthesize MLNPs due to their piezo-photonic effects.[126–128] Notably, biocompatible MLNPs synthesized from non-toxic elements have been developed to emit blue light, serving as an internal light source for optogenetics.[106,108,109] Hong et al. pioneered the use of sonooptogenetics, which combines mechanoluminescent properties with focused ultrasound (FUS), offering a promising alternative in neuroscience due to the intense light transmission produced by FUS (light intensity more than 5 times).[106,108,109,125] These phosphors, synthesized by the bioinspired demineralization (BID) strategy, emit bright blue light and are effective for transcranial afterglow imaging and optogenetics (Figure 4d–f). The BID-derived colloidal solutions allow for deeper tissue penetration and a wider field of view in afterglow imaging than traditional methods. This technique eliminates the need for external excitation, thereby reducing scattering and autofluorescence, and enabling non-invasive imaging through an intact skull (Figure 4g). These colloids offer a minimally invasive approach to optogenetics, with the potential to modulate gene expression and neural activity without the need for cranial windows or implanted lenses in the brain (Figure 4h). Indeed, a significant increase in c-fos$^+$ cells was observed in Thy1-ChR2-yellow fluorescent protein (YFP) transgenic mice, which express ChR2 in neurons, compared to wild-type (WT) C57BL/6J mice (Figure 4i–k). Despite overcoming the above-mentioned limitations of UCNP-based optogenetic systems, MLNPs still face challenges related to the recharging process near superficial blood vessels. Biological factors such as tissue heterogeneity, thickness, and blood flow can impact the uniformity of light distribution and efficiency of light delivery, especially in the spectral of UV light, which was employed to recharge MLNPs.[41,99]

3.3. Plasmonic Nanoparticles

Plasmonic nanoparticles and photothermal agents are materials that convert absorbed light into heat, which can be harnessed for various biomedical applications, including bioimaging [129,130] and cancer therapy [131,132] (**Figure 5a,b**). When exposed to NIR light, these agents generate localized heat, leading to the destruction of targeted cells, such as cancer cells, by hyperthermia. This process, known as photothermal therapy (PTT), provides a minimally invasive treatment option with high specificity and controlled thermal effects (Figure 5c). Recent progress was focused on enhancing the biocompatibility, targeting efficiency, and thermal stability of these agents. Additionally, there is ongoing research into combining photothermal agents with other therapeutic modalities, such as chemotherapy, immunotherapy, and optogenetics, to improve the therapeutic efficacy.[133,134] In optogenetics, for example, the ectopic expression of transient receptor potential cation channel subfamily V member 1 (TRPV1) channels in mouse retinal cones has endowed vision through the resonant absorption of gold nanorods (AuNRs) (Figure 5d–f).[110] Hong et al. developed the most advanced optogenetic system using NIR-II photothermal neural stimulation, which showed the activation of neurons through the skull of freely moving mice via a tether-free, implant-free interface (Figure 5g).[111] Their semiconducting polymeric nanoparticles, known as macromolecular infrared nanotransducers for deep-brain stimulation (MINDS), sufficiently activated heat-sensitive TRPV1 channels in neurons with the highest NIR-II absorption efficiency at low laser power densities (Figure 5h,i). The in vivo onset and offset latency times for neuromodulation in the secondary motor cortex (M2) were 5.0 ± 1.5 s and 10.7 s under NIR-II irradiation from a distance of 50 cm above the mouse head, which were faster than those observed in magnetothermal and chemogenetic neuromodulation.[135,136] They also demonstrated a significant increase in neuron firing rate and behavior manipulation in the hippocampus, M2, and VTA of freely behaving animals, with minimal chronic gliosis in the neural tissue. The significant notification was that they validated the necessity of TRPV1, MINDS, and 1064 nm light for effective photothermal neuromodulation in the brain at depths up to 6 mm without restricting the natural behavior of mice (Figure 5j,k). However, the invasive intracranial injections required for TRPV1 and MINDS pose similar levels of invasiveness to other neuromodulation techniques. In addition, the latency times of in vivo NIR-II neuromodulation were slower than those of optogenetics for activating excitatory opsins,[137] and the unexpected heating of brain tissue might suppress nerve activity or induce other negative side effects.[101]

4. Wearable Photonic Devices for Photobiomodulation

Wearable photonic devices for photomodulation represent an emerging field of non-invasive technologies designed to deliver controlled light directly to the body.[138,139] These devices leverage advanced photonic materials, such as micro-LEDs (μLEDs) and laser diodes, integrated into flexible, lightweight, and comfortable wearables that can be applied to the skin, eyes, or even clothes.[43,140–142] The primary function of these devices is to emit the specific wavelength of light, typically in the red or NIR range, to achieve photobiomodulation. This modulation of cellular activity leads to various therapeutic effects, including tissue regeneration, pain relief, and anti-inflammation.[19,138,139] The mechanism underlying photobiomodulation is based on the biological function of cytochrome C oxidase (CCO) within mitochondria. In addition, photobiomodulation can control the immune response by enhancing M2 macrophage polarization and lead to anti-inflammation for wound healing,[13,27,28,143] providing a potential link to neuro-immune modulation. The neuromodulation through calcium ion influx in neurons has also enabled the application of photobiomodulation in neuroscience,[29] offering precise control over neuro-immune interactions and the targeted treatment for a range of neurological disorders. This technique has shown significant promise in addressing brain injuries and



promoting neural regeneration by selectively activating specific neural circuits with light.[15–17] The rise of wearable photonic devices, such as photonic patches and smart contact lenses, is set to revolutionize this field by enabling precise, non-invasive, and personalized light-based treatments. These innovations enhance the effectiveness of photobiomodulation, providing continuous and controlled light delivery to targeted neural circuits, and offer new great opportunities for treating a wide range of neurological disorders with neuro-immune interaction.

4.1. Wearable Photonic Patch Devices

Wearable photonic patch devices are based on rigid photonic components such as μLEDs, photodetectors, and integrated-circuit chips on stretchable thin substrate platforms (**Figure** 6a,b).[142,144,145] These devices utilize innovative designs, including serpentine electrodes, to fabricate flexible electrical connections that maintain functionality even under mechanical stress such as stretching or bending. Additionally, buckling and wavy structures have been introduced into thin film devices to make stretchable light sources and detectors (Figure 6c).[146–148] Organic LEDs (OLEDs) (Figure 6d) have been designed with high performance and stretchability,[149–151] and photonic wearable devices have been fabricated using intrinsically stretchable photonic materials (Figure 6e).[152–154] This flexibility enables conformal contact to the body's contour, ensuring uniform illumination across large areas and seamless integration with the skin for enhanced therapeutic efficacy. These wearable devices incorporated with OLEDs further serve as effective surface light sources for wearable biophotonic applications, particularly for photobiomodulation therapy (Figure 6f,g).[155,156] By emitting light in the red to NIR spectrum, these devices can penetrate biological tissues and stimulate mitochondrial chromophores, leading to increased cell proliferation, accelerated wound healing, and other beneficial therapeutic effects.[140,145,157] For example, flexible OLED patches have been developed as band-type wound-care devices, showing a significant improvement in fibroblast migration and the recovery of deep wounds.[158]

The capability of wearable photonic patches to provide high performance with low power consumption and minimal heat generation makes them ideal for long-term use on the skin. These characteristics help to minimize thermal damage to cells, making the patches suitable for long-term continuous therapeutic application. In addition, they allow for non-invasive targeted treatments throughout daily activities, enhancing patient compliance and treatment adherence. Although wearable photonic patches have numerous advantages, they face certain limitations, particularly in the realm of neurostimulation. Despite the excellent surface-level treatments and light delivery, the patch-type design may not provide the depth of light penetration or precision required for effective neurostimulation in barrier tissues.[99,100] This limitation suggests that while wearable photonic patches are highly effective for various therapeutic applications, including wound healing and photobiomodulation, they should be combined with other modalities or advanced technologies for comprehensive neurostimulation treatments. Remarkably, Hong et al. have developed a remarkable approach to enhance optical transparency in live biological tissues.[159] By using absorbing molecules like tartrazine, an FDA-approved food dye, they reduced light scattering caused by mismatched refractive indices in tissue components. This technique enabled deep-tissue visualization of internal organs such as the liver, intestines, and cerebral blood vessels in live rodents without invasive procedures. The transparency effect was reversible and safe, opening up new possibilities for advancing phototherapy applications using wearable photonic patches. In the context of skin, where sensory neurons play a key role as immunoregulators, it is anticipated that enhancing sensory neuroregeneration would pave the way for future studies on neuro-immune cross-talks.

4.2. Wearable Photonic Contact Lenses

Wearable photonic contact lenses are at the forefront of innovation in healthcare, offering a unique and versatile platform that bridges the gap between non-invasive diagnostics and therapeutic interventions.[160–162] These photonic contact lenses integrate cutting-edge photonic technology, including μLEDs and photonic crystals, into a compact, wearable form factor that interfaces directly with the eye (**Figure** 7a). This interface provides a seamless connection between the device and the body, leveraging the natural sensitivity of eyes to light (Figure 7b,c). In the realm of treatment, wearable photonic contact lenses have shown significant potential in addressing ocular diseases through photobiomodulation.[19,138,163–165] It involves the use of a specific wavelength of light to modulate cellular activity, promoting healing and reducing inflammation. Park et al. have demonstrated red OLED contact lenses to protect retinal pigment epithelial (RFE) cells from damage caused by lipofuscin-blue light (Figure 7d).[19] The exposure to red light decreased the ROS in cells,[166] potentially delaying cell death and preserving vision.

Figure 4. MLNPs for optogenetics. a) Schematic illustration for sono-optogenetics, showing the circulation of MLNPs in the bloodstream and the conversion of 400-nm photoexcitation energy into 470-nm emission in deep brain regions under FUS stimulation. b) The underlying mechanism of ultrasound-triggered light emission from MLNPs. c) Measurement of 470-nm light emission intensity from MLNPs under repeated FUS stimulation (red ticks) and continuous 400-nm recharging light (violet bar). Reproduced with permission,[106] Copyright 2019, National Academy of Sciences. d) Afterglow and bright-field (inset) images of bulk particles compared to BID-derived MLNPs. BID-derived MLNPs are utilized as an intravital light source for e) transcranial afterglow imaging and f) YFP afterglow imaging. Reproduced with permission,[109] Copyright 2018, American Association for the Advancement of Science. g) Photo image of the in vivo sono-optogenetic stimulation setup. h) Photo images and hindlimb movement analysis of a Thy1-ChR2-YFP mouse during sono-optogenetic stimulation through an intact scalp under different conditions. In the top images, red and black lines represent the movement of the left and right hindlimbs, respectively, while the bottom kinematic diagrams highlight contralateral limb activation during sono-optogenetic stimulation in red. Reproduced with permission,[106] Copyright 2019, National Academy of Sciences. i) Schematic illustration of in vivo ultrasound-mediated optogenetic stimulation using MLNPs in the M2 of the brain. j) Confocal images showing c-fos (left), ChR2-YFP (middle), and their overlay (right) in the M2 region in Thy1-ChR2-YFP (top) and WT (bottom) mice under different conditions. All scale bars represent 40 μm. k) Statistical analysis of c-fos$^+$ cells in Thy1-ChR2-YFP and WT mice in (j). Data are presented as mean ± standard deviation (SD) ($n = 3$, $^{***}p < 0.001$). Reproduced with permission,[108] Copyright 2022, American Chemical Society.

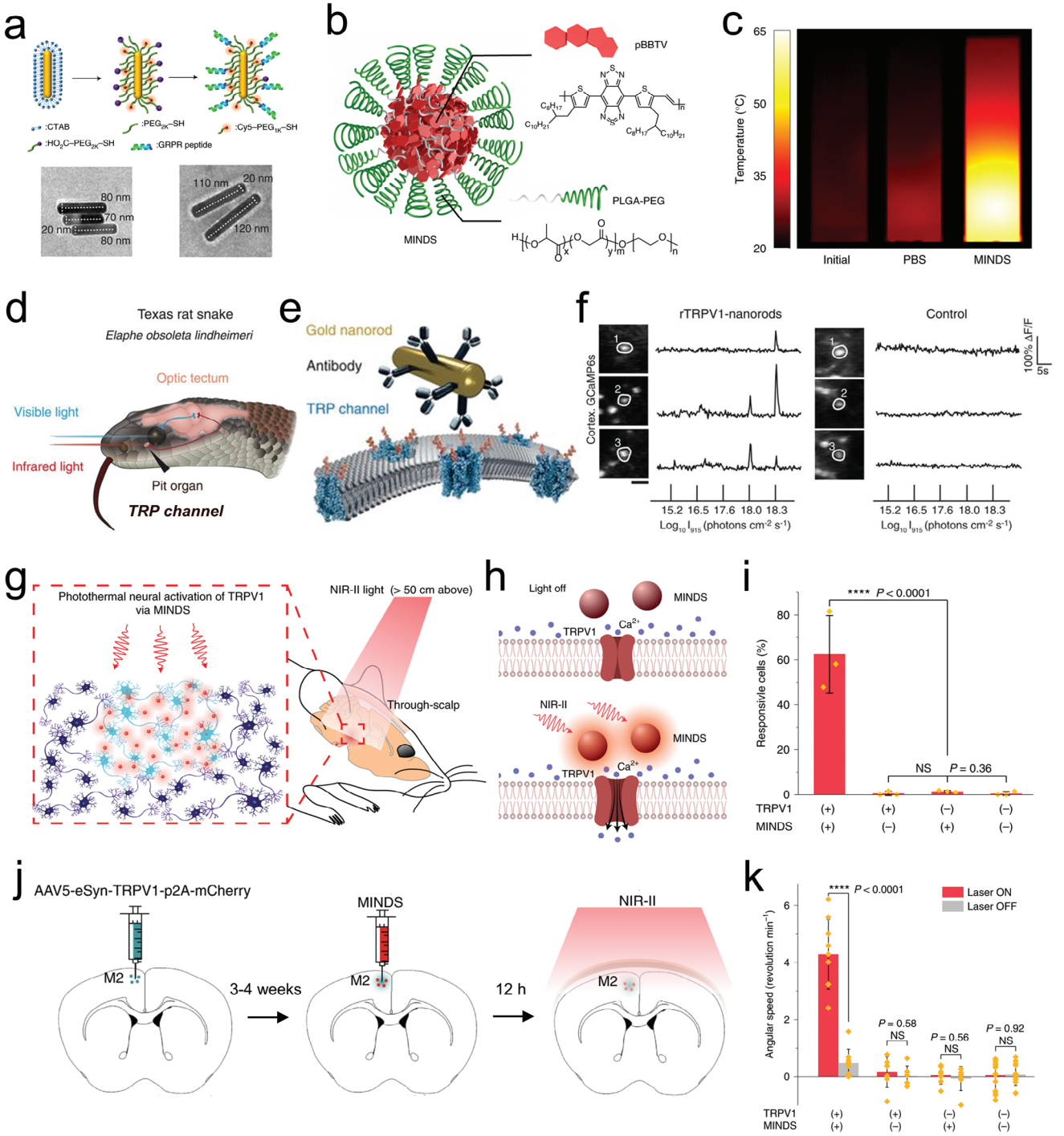


Figure 5. Plasmonic nanoparticles for optogenetics. a) Schematic illustration and TEM images depicting plasmonic metal nanoparticles, AuNRs. Reproduced with permission,[132] Copyright 2019, Springer Nature. b) The composition of plasmonic polymeric nanoparticles, MINDS. c) Thermal images showing the photothermal heating efficiency of MINDS under NIR-II light irradiation. Reproduced with permission,[111] Copyright 2022, Springer Nature. d) The location of the TRPV1-expressing, infrared-sensitive pit organ with the information overlaid on the optic tectum. e) The engineered TRPV1 (blue) expressing protein epitope tags (orange) in extracellular domains and binding with antibody-conjugated AuNRs. f) Two-photon images and calcium responses to 915-nm light stimulation recorded in mice transduced with TRPV1 and AuNRs compared to control. The scale bar represents 25 μm. Reproduced with permission,[110] Copyright 2020, American Association for the Advancement of Science. g) Through-scalp neuromodulation with NIR-II light irradiation from a distance of 50 cm above the mouse head, which triggers TRPV1 activation through MINDS. h) Schematic illustration showing NIR-II photothermal activation of TRPV1 located in the cell membrane, mediated by MINDS. i) Proportion of cells responding to NIR-II light irradiation. Data are presented as mean ± SD (n = 3, ****$p < 0.0001$). j) The process of TRPV1 virus delivery (left), MINDS injection (middle), and NIR-II activation of TRPV1 neurons through the scalp (right). k) Statistical analysis of rotational movements in animals under different experimental conditions. Data are shown as mean ± SD ($n = 6$, ****$p < 0.0001$). Reproduced with permission,[111] Copyright 2022, Springer Nature.

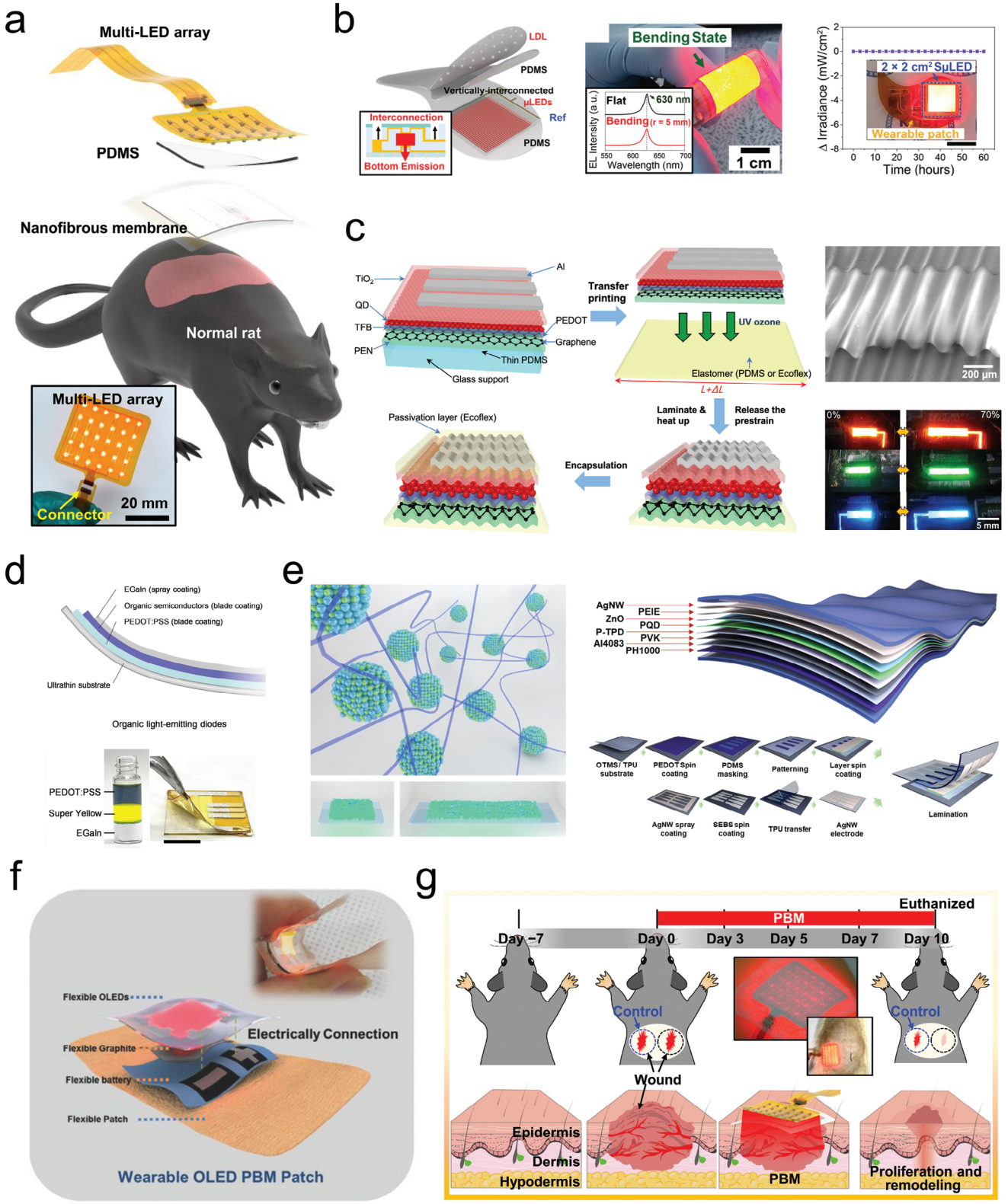


Figure 6. Wearable photonic patch devices for photobiomodulation. a) A rigid, multi-LED array integrated with stretchable substrates. Reproduced with permission,[139] Copyright 2022, American Association for the Advancement of Science. b) Schematic illustration and photo images showing the stable operation of μLED patch under bending state. Reproduced with permission,[145] Copyright 2022, John Wiley & Sons. c) The fabrication process for creating stretchable LED devices with a wavy configuration and photoimages of stretchable red, green, and blue LEDs at 0% to 70% strains. Reproduced with permission,[147] Copyright 2017, American Chemical Society. d) The structure of OLEDs and their fabrication process on an ultrathin substrate. The scale

Moreover, Hahn et al. have embedded far-red/NIR LEDs in the lenses with wireless power and communication systems for the treatment of diabetic retinopathy (Figure 7e).[138] These lenses significantly reduced retinal vascular hyper-permeability induced by diabetic retinopathy in rabbits with the regular use of far-red/NIR LED contact lens for 8 weeks under 120 μW light irradiation for 15 min per day, three times a week. This represents a major advancement over traditional therapies, which often require more invasive approaches.

The unique advantage of wearable photonic contact lenses lies in their ability to provide non-invasive, continuous monitoring and treatment from the eyes to the brains. Unlike traditional methods that involve the implantation of optical fibers with the risk of inflammation, immune activation, and glial scar formation,[102,103] these lenses offer a safer, more patient-friendly alternative. Their non-invasive nature minimizes the risk of complications, while their direct connection to the CNS via the optic nerve opens new possibilities for treating neurological disorders.[19,161] For instance, in a model of Alzheimer's disease, photobiomodulation[31] and optogenetics[30,167] have been used to reduce amyloid-β plaques and improve cognitive function by modulating microglial activity (Figure 7f,g). In addition, photonic contact lenses can modulate precise control over neuronal circuits and enhance neuroregeneration. A recent study demonstrated that optogenetic activation of retinal ganglion cells can stimulate the visual cortex, reflecting the feasibility of light-based neurostimulation for treating neurodegeneration.[168] By integrating these approaches, a smart contact lens would serve as a light delivery tool for non-invasive neural stimulation and immune regulation. However, there are some technical hurdles for smart photonic contact lenses to stimulate various nerves, including brains, lungs, and guts. As a result, advanced implantable photonic devices would offer higher efficiency in neurostimulation and immune regulation in barrier tissues, providing more effective therapy for neurological disorders.

5. Implantable Photonic Devices for Optogenetics

Implantable photonic devices capable of interfacing with the nervous system hold great potential for health monitoring, diagnosis, and treatment of various neurological disorders and injuries.[169,170] While traditional approaches using external light sources restrict the study of complex neural activities in naturally moving animals, wireless and battery-free implantable optogenetic devices greatly minimize behavioral disruptions. This enables researchers to expand the scope of their experiments with greater accuracy and minimal interference. The incorporation of μLEDs and radiofrequency (RF) with magnetic coupling strategies enables miniaturization and accomplishment of wireless, battery-free, and fully implantable photonic devices for various optogenetic neuronal applications. From these advances in wireless photonic devices, the additional integration with pharmacological systems, electrochemical or physical sensing systems enables complicated neuronal research. Recently, wireless and implantable photonic devices for optogenetics have been focused on the brain and spinal cord stimulations. However, there remains significant potential to expand these technologies to target other areas, including the gastrointestinal system, direct nerves, and the stomach.[171,172] Addressing these challenges will significantly enhance the capability of these systems to manipulate and study neural circuits throughout the body, offering new insights into neuro-immune interactions for neuroimmunotherapy.

5.1. Optoelectronic Flexible Devices

Optoelectronic flexible devices have been widely investigated for various biomedical applications.[44,173–175] Among them, μLEDs are one of the promising light sources for miniaturized optoelectronic devices. The small size of optoelectronic devices with μLEDs can provide direct implantation on the top of the skull (head-mounted designs) or spinal cord (back-mounted designs) without any impedance of behaviors in animals as small as mice (**Figure 8a,b**).[44,173–175] The μLEDs integrated with the needle-shaped probe can deliver light locally and selectively into the target sites with high efficiency.[176] In addition, the μLEDs arrays can deliver light to the large target area like full organ-scale dimensions over ≈ 150 cm^2 (Figure 8c).[177–179] With the progress of stretchable and flexible electronics, optoelectronic devices can be conformally and directly integrated into the organ surfaces or nerves without mechanical mismatch between organs and devices. This conformal and direct light delivery enables to enhance the efficiency of the light delivery and minimizes the damage to both organs and devices (Figure 8d).[179–181]

The programmable optogenetics can be available by a single device incorporated with different μLEDs. The different μLEDs are turned on individually or simultaneously for the optogenetic stimulations in unilateral, bilateral, or multilateral designs (Figure 8e).[182] For instance, the unilateral dual μLEDs with different wavelengths simultaneously offer co-expressed opsins (ChrimsonR and stGtACR2) (Figure 8f).[183] In other cases, the defensive behaviors of animals are controlled by injecting unilateral μLEDs systems with the same wavelength into the different depths of brains.[51,184,185] Multilateral μLEDs systems permit advanced real-time subject- or user-specific programmability, controlling the motor behaviors and social interaction in the groups of animals (Figure 8g).[173,182] However, these inorganic μLEDs systems are generally demonstrated by passive structures, which can limit the number of light sources for more complicated investigations of neuroscience. To address this limitation, active structures including complementary metal-oxide-semiconductor (CMOS) technologies can be introduced for the scalable LED-integrated optogenetic systems that can separately stimulate different neurons (Figure 8h).[178,186]

bar represents 1 cm. Reproduced with permission,[151] Copyright 2024, American Association for the Advancement of Science. e) Schematic illustration and fabrication process of a stretchable perovskite LED emitting layer. Reproduced with permission,[153] Copyright 2024, Springer Nature. f) Wearable photobiomodulation patch with flexible OLEDs and substrates, utilizing a lamination structure. Reproduced with permission,[158] Copyright 2022, John Wiley & Sons. g) Schematic illustration of the wound healing process using red-light emitting wearable photonic patches for photobiomodulation. Reproduced with permission,[139] Copyright 2022, American Association for the Advancement of Science.

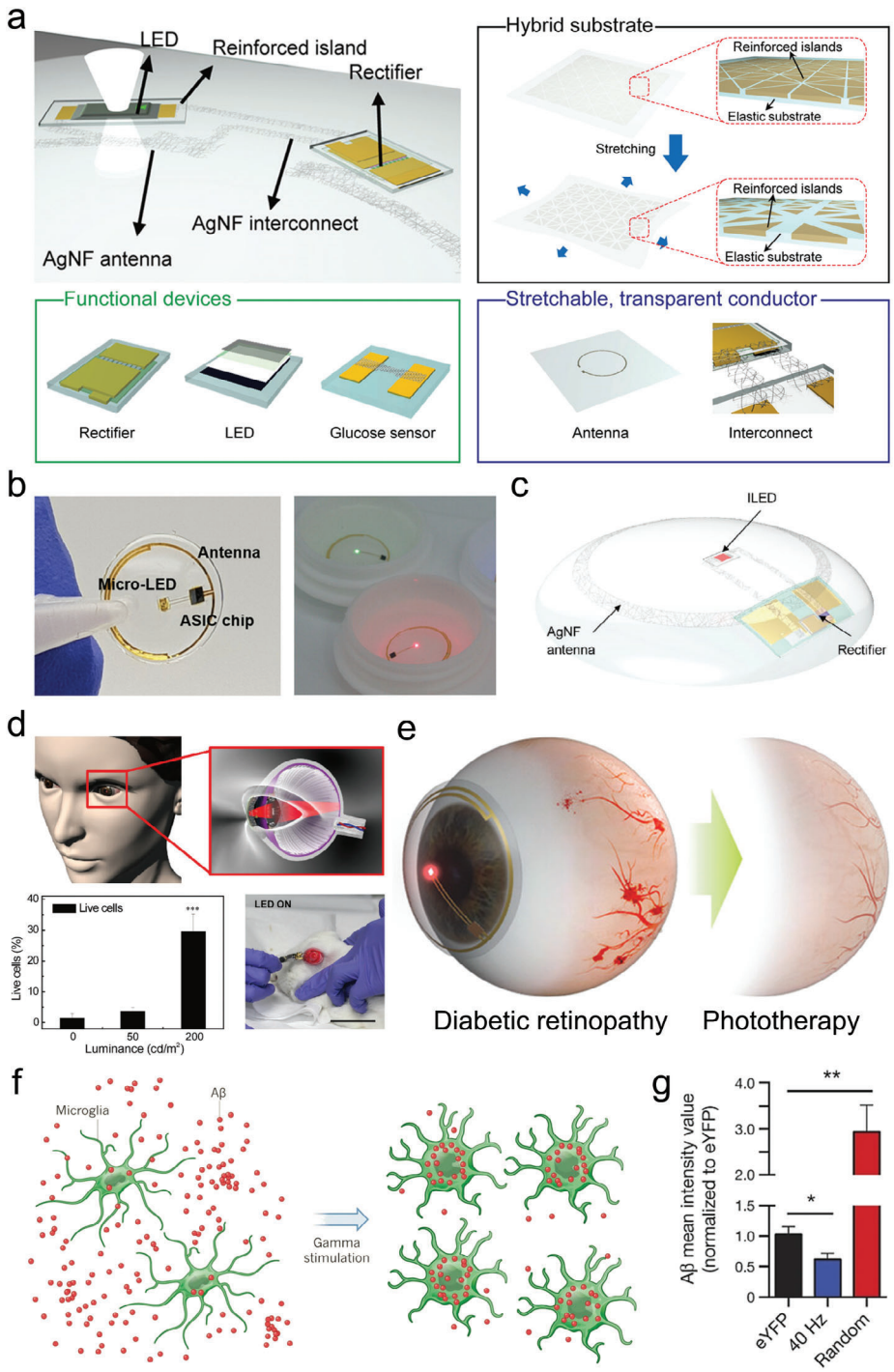


Figure 7. Wearable photonic contact lenses for photobiomodulation. a) Schematic illustration of a wearable photonic contact lens, composed of a hybrid substrate, functional device, and a stretchable, transparent conductor. Reproduced with permission,[160] Copyright 2018, American Association for the Advancement of Science. b) The photoimages of a μLED integrated smart contact lens and wirelessly controlled red, green, and blue (RGB) color lighting of the contact lenses. Reproduced with permission,[138] Copyright 2022, John Wiley & Sons. c) Soft contact lens-based phototherapeutic devices integrated with inorganic-LED (ILED). Reproduced with permission,[19] Copyright 2019, Springer Nature. d) Schematic illustration of red-light therapy targeting the retina, showing the percentage of live cells following red OLED treatment. Data are shown as mean ± SD ($n = 3$, $^{***}p < 0.001$). A photo image shows the photonic contact lens on the eye of live rabbits and the light emission with wireless power transfer. The scale bar represents 5 cm. Reproduced with permission,[19] Copyright 2019, Springer Nature. e) Schematic illustration of diabetic retinopathy treatment using a red-light emitting photonic contact lens for photobiomodulation. Reproduced with permission,[138] Copyright 2022, John Wiley & Sons. f) Schematic illustration depicting optogenetic modulation of microglial activity for Alzheimer's treatment. Reproduced with permission,[167] Copyright 2016, Springer Nature. g) Reduction of immunoreactivity of amyloid-beta (Aβ) plaques. Data are shown as mean ± SEM ($n = 3$, $^{*}p < 0.05$, $^{**}p < 0.01$). Reproduced with permission,[30] Copyright 2016, Springer Nature.

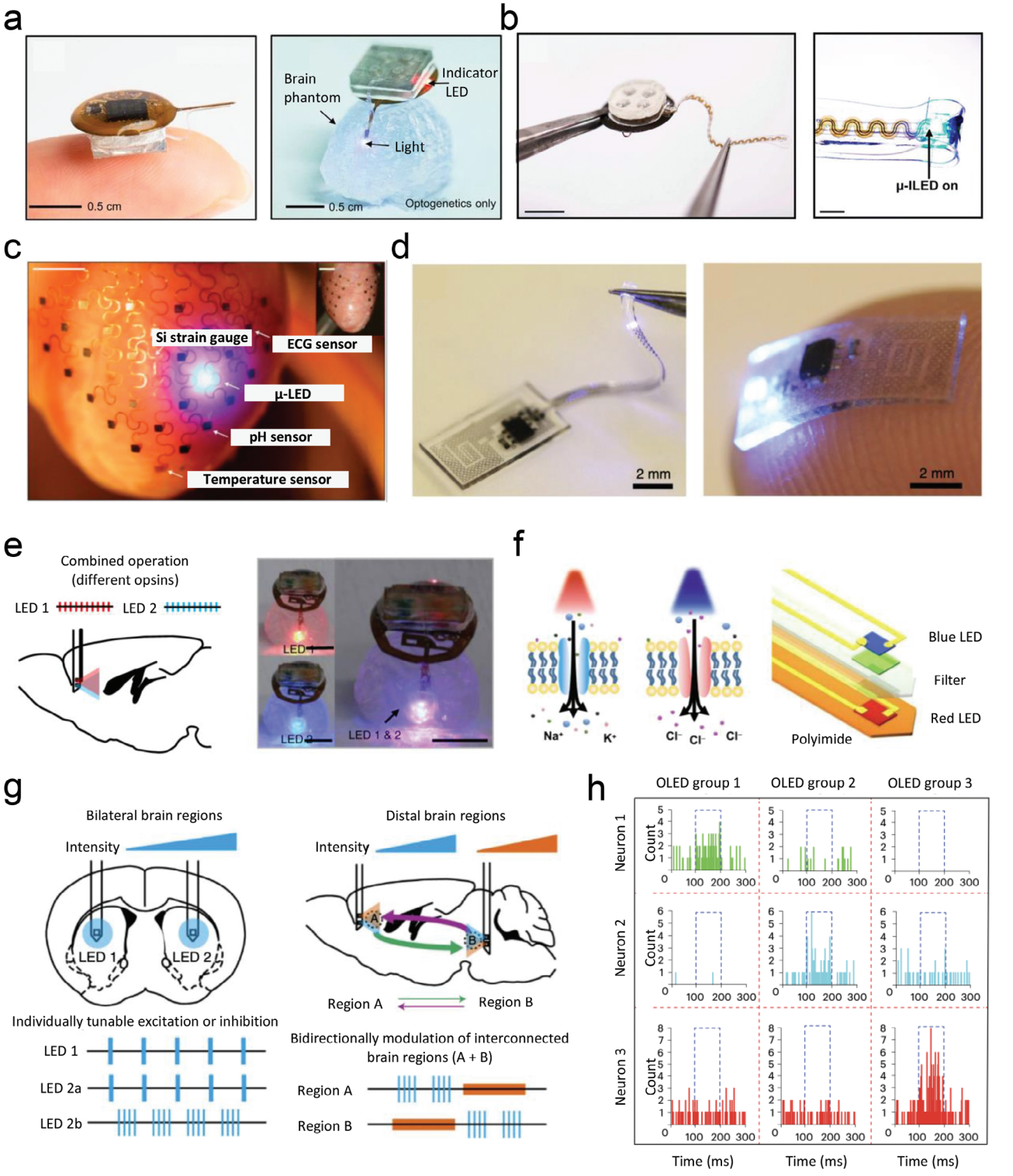


Figure 8. μLEDs-integrated a) wireless optogenetic systems, Reproduced with permission,[44] Copyright 2021, Springer Nature and b) 3D structured cuff systems, Reproduced with permission,[180] Copyright 2019, American Association for the Advancement of Science. c) Flexible and stretchable 3D multifunctional optogenetic systems. Reproduced with permission,[179] Copyright 2014, Springer Nature. d) μLEDs-integrated miniaturized optogenetic systems. Reproduced with permission,[181] Copyright 2015, Springer Nature. e) μLEDs-integrated dual-color optoelectronic probe, Reproduced with permission,[183] Copyright 2022, Springer Nature and f) wireless optogenetic device, Reproduced with permission,[182] Copyright 2022, Springer Nature. g) Wireless multilateral optogenetic devices. Reproduced with permission,[173] Copyright 2021, Springer Nature. h) Matrix of the firing histogram of each neuron during stimulation pulses applied by different OLEDs-integrated optogenetic probes. Reproduced with permission,[186] Copyright 2023, Springer Nature.

5.2. Optogenetic Systems

Battery-powered optogenetic systems are able to offer stable power transfer to implantable optogenetic systems. However, these systems have several critical limitations such as significant weight and bulky size, limiting the experimental options.[187] In accordance, wireless and battery-free optogenetic systems that can remotely control the programmable optogenetic stimulations are highly needed for the investigation of the complicated experimental scope of neuroscience.[188,189] RF-based magnetic resonant coupling at 13.56 MHz of industrial, scientific, and medical (ISM) band has been generally used for wireless and battery-free optogenetic systems with high power (5-10 mW). Far-field power delivery system is another choice for RF-based power transfer systems with a low level of RF power (3-5 mW) (**Figure 9a**).[190,191] However, these systems passively modulate the RF source, restricting real-time modification of stimulation protocols, and the power efficiency is significantly decreased with increasing distances between transmission coils and receive coils.[192] In addition, it's not possible to achieve precise regulation and programmable bilateral or multilateral systems for activating two distinct opsins. The active electronic circuits including RF Schottky diodes and a linear dropout regulator (LDO) can be introduced to precisely and separately control the optogenetic stimulations (Figure 9b).[193,194] Because the RF-based coil-powered systems suffer from the short operation distances, self-powered systems including photovoltaics[195,196] and triboelectric nanogenerators[197,198] are incorporated into the optical stimulation systems (Figure 9c). Nevertheless, it still has several critical challenges of fragile nature, stability under physiological conditions, and biocompatibility of materials, which should be addressed for translational medical applications.

The control module and data analytic systems enable coordinated and user-friendly closed-loop operations.[90,199] The common closed-loop systems with concurrent electrical recordings and electrical stimulation systems limit the precise control protocols because the electrical sensing and stimulation generally occur at the same site.[200] The closed-loop optogenetic systems enable the precise and real-time manipulation of neurostimulations with the extensive data processing and control module without any impedance of electrical recordings and optostimulations.[201,202] Some sensors integrated with optogenetic systems transfer wirelessly physiological signals to user interfaces and optogenetic stimulations can be manipulated depending on the physiological signals in real-time. For instance, strain sensors can monitor organ behaviors such as bladder volume changes or cardiac movements, and electrochemical sensors can monitor catecholamine (Figure 9d).[38,203] Other external EMG sensors, muscle force sensors, and algorithms exhibit more precise control of optogenetic stimulations.[33,204,205] In addition, different optogenetic stimulation with different colors of μLEDs can control the activation and silence of muscle responses, enabling the reconstruction of leg movements (Figure 9e). This type of closed-loop optogenetic system helps patients and medical specialties to plan and modify therapeutic strategies, maximizing therapeutic effects and minimizing side effects for futuristic precise medicine.

For effective optogenetic stimulation, light intensity is crucial to activate opsins without causing tissue damage. For ChR2, 0.1–10 mW mm^{-2} at ≈470 nm is sufficient for neuronal activation without phototoxicity.[206] NpHR requires 1–5 mW mm^{-2} at ≈590 nm for inhibition,[207] and Arch needs 1–5 mW mm^{-2} at ≈520-550 nm for inhibition,[208] but higher intensities must be carefully managed to avoid thermal damage. Since the optical sources including NIR light and μLED can cause thermal damage depending on the power intensity, ensuring thermal safety across different target sites is crucial. Even small temperature increases (below 1 °C) can affect neural activities.[101] Simulation studies would play a key role in optimizing parameters like intensity, scope, and duration to enhance therapeutic effects while minimizing side effects. Additionally, the implanted photonic devices can affect the local immune responses like foreign body reaction (FBR) with negative side effects such as vomiting, headache, inflammation, and so on. In this context, biocompatible nanoparticles and noble approaches including nonimmunogenic neural interfaces have been designed to avoid the negative side effects.[38,109,209] There is also a strong need to study the immunotoxicity of devices in both small and big animals, considering their differing immune systems.[121] On the other hand, short bursts of light can quickly modulate neuronal activity, whereas long-term stimulation may induce changes in synaptic plasticity or opsin desensitization. While most optogenetic research using implantable photonic devices has focused on behavior regulation, the current technology offers the potential for neurostimulation. With the capability to adhere well to organ surfaces, these devices would be implanted in barrier tissues to enable immune regulation and provide in-depth monitoring of immune responses. This advancement will open up new possibilities for analyzing neuro-immune interactions in complex systems.

6. Translation of Photobiomodulation and Optogenetics

The translation of photonic nanomaterials and devices for medical applications involves leveraging light-based technologies to precisely control and modulate neural activity. These materials, such as UCNPs and metal nanoparticles, are being developed for optical neuromodulation, where the choice of optical method, device placement, and localization are critical for achieving effective and targeted treatment (**Table 1**). Photonic devices offer significant potential to modulate immune responses, particularly in barrier tissues like the skin, brain, and gut, where they can help regulate inflammation and promote healing, minimizing invasiveness. However, further research on neurostimulation using photonic nanomaterials and devices, along with their roles in immune regulation, is essential for their translation into clinical applications.

From the perspective of photomedicine, photobiomodulation lacks sufficient exploration in linking neuron stimulation to immune responses, creating a gap in understanding neuro-immune interactions. While it has been effective for therapies related to wound healing and immune regulation,[31,139] its role in modulating immune functions through neuronal activation or inhibition remains immature. To advance this field, further studies are necessary to explore how photobiomodulation can specifically regulate neuro-immune interactions, providing important insight into immune modulation for therapeutic applications in inflammatory or neurodegenerative conditions. This would mark

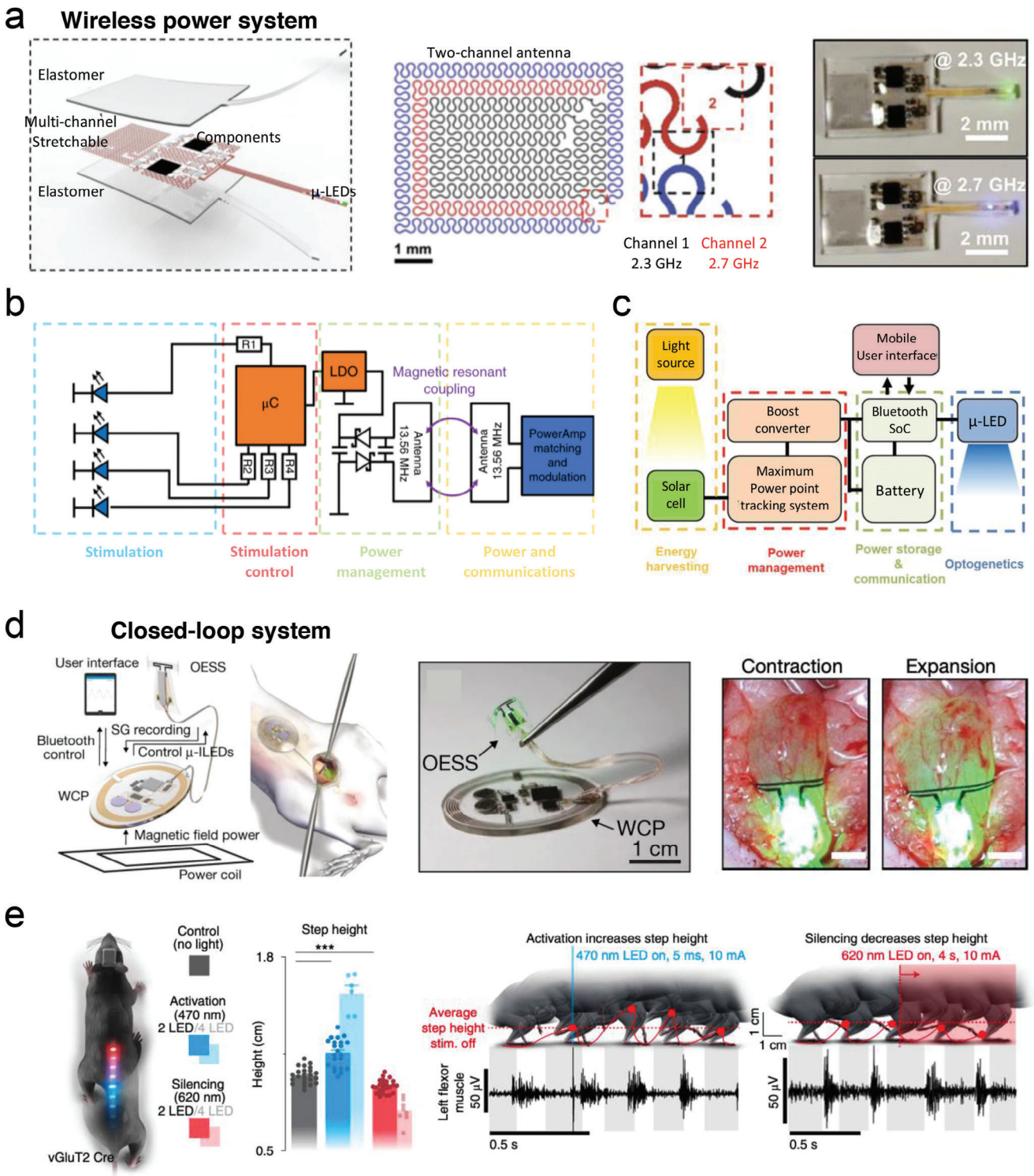


Figure 9. Wireless power systems and closed-loop systems for optogenetics. a) Multichannel energy harvester components for the optogenetic systems. The wireless harvester activates green and blue μLEDs with different frequencies. Reproduced with permission,[190] Copyright 2016, National Academy of Sciences. Electrical schematics for b) active power regulation and digital control for optogenetics, Reproduced with permission,[193] Copyright 2018, Springer Nature and c) solar-powered optoelectronic systems, Reproduced with permission,[195] Copyright 2023, American Association for the Advancement of Science. d) Wireless and closed-loop optogenetic systems for bladder monitoring and peripheral neuromodulations. Reproduced with permission,[38] Copyright 2019, Springer Nature. e) Wireless closed-loop optogenetic systems for the dorsoventral spinal cord. Reproduced with permission,[33] Copyright 2021, Springer Nature.

Table 1. Photonic nanomaterials, and wearable and implantable photonic devices for therapeutic applications via the neuro-immune cross-talks at the barriers in the body.

Tools	Methods	Localized therapy	Pros	Cons	Refs.
Photonic nanomaterials	Administration (blood circulation and accumulation) & focused ultrasound	Brain, lung, and gut barriers	– Precise control – Minimally invasiveness – Deep tissue penetration – Scalable and customizable – Potential for multi-modal therapy	– Limited light penetration – Potential toxicity – Complex delivery mechanisms	[104,116]
	Transdermal delivery & NIR light	Skin barriers			
Wearable photonic devices	Smart contact lenses	Through eyes	– Non-invasiveness – Ease of use – Continuous delivery – Localized treatment – Programmability	– Comfort and wearability issues – Limited depth of delivery	[139]
	Wearable patches	Through skins			[138]
Implantable optoelectronic devices	Optical probes 3D structure designs Stretchable optical source Conformal interfaces	Target adherence or implantation	– Highly efficient optical delivery – Precise control of intensity and duration – Long-term operation – Programmable and controllable optical delivery of different wavelengths – Facile integration with other components	– Thermal safety issues – Invasiveness – Bulky size – Limitations of optical delivery at deep and local tissue – Tissue damage	[171,181] [180,205] [186] [87]

an essential step in broadening the applications of photobiomodulation within neuro-immunology. On the other hand, a notable clinical milestone using ChrimsonR in retinal cells achieved partial vision restoration in a blind patient, underscoring the potential of optogenetics in disease treatment.[40]

However, there are several challenges for the clinical translation of optogenetics, including safety concerns with viral vectors, difficulties in light delivery to deep-seated areas,[99] cell-specific opsin delivery, and concerns about long-term safety and efficacy. Nevertheless, emerging strategies would successfully address these issues. Non-viral and transient gene delivery methods can minimize safety concerns associated with viral vectors.[210] Furthermore, NIR-light specific nanoparticles, optical agents for transparency, wireless optogenetic devices, and transcranial light delivery systems could enhance light delivery to deep tissues.[41,159] Notably, advances in tissue-specific promoters and cell-targeting peptides are also promising for ensuring precise opsin activation.[211,212] Moreover, the development of biodegradable materials and reversible opsin expression systems can mitigate the issues related to chronic stimulation and immune reactions.[92] Lastly, rigorous preclinical testing in large animal models is crucial for translational research to human trials in consideration of the difference in the immune system complexity between small and large animals.[44] These advancements are essential for bringing optogenetic therapies closer to clinical applications.

7. Summary and Perspectives

In this *Perspective*, we overview and discuss the emerging field of neuroimmunology, highlighting the intricate interactions between the nervous and immune systems, which are crucial to maintaining homeostasis and responding to diseases. The concept of neuroimmunology has gained great attention, as the relevant research reveals how the nervous system can regulate the immune system, particularly in barrier tissues like the brain, skin, lungs, and intestines. Immune responses are influenced by neuronal activation and inhibition, making optogenetics, which allows for selective activation or inhibition of neurons using various opsins, a focal point in neuroimmunology.[12,13,39,213] Although optogenetic neurostimulation for immune regulation is now under investigation, there is a notable lack of exploration into the neuro-immune cross-talks facilitated by photonic nanomaterials and devices. In accordance, this *Perspective* covers photonic nanomaterials and devices currently used in photobiomodulation and optogenetics for digitally controlled neurostimulation, providing the potential for neuro-immune interactions. A variety of photonic nanomaterials, such as UCNPs, MLNPs, and plasmonic metal nanoparticles, have been developed to offer improved efficiency and less invasive alternatives for neural modulation. In addition, the development of wearable photonic devices for photobiomodulation is explored as a non-invasive therapy that uses light to modulate cellular activity. These flexible and wearable devices are promising in treating neurological disorders, promoting tissue regeneration, and providing pain relief through targeted light therapy. Moreover, the development of implantable photonic devices is further highlighted, which presents another avenue for advancing neural modulation. These photonic devices, capable of delivering light deep within the body, are designed to offer precise control over neural activity with high efficiency compared to non-invasive methods. Implantable photonic devices are particularly advantageous in cases where deep brain regions need to be targeted, or where sustained and localized light delivery is critical for therapeutic outcomes. Given that technologies for neurostimulation are already in place, there is a growing expectation for focused research on immune regulation through neuronal stimulation. This would pave the way for innovative diagnostics and treatments for diseases based on neuro-immune interactions.

The intersection of neuroimmunology and advanced photonic technologies represents a promising frontier in biomedical research (**Figure 10**). The continued development of both wearable

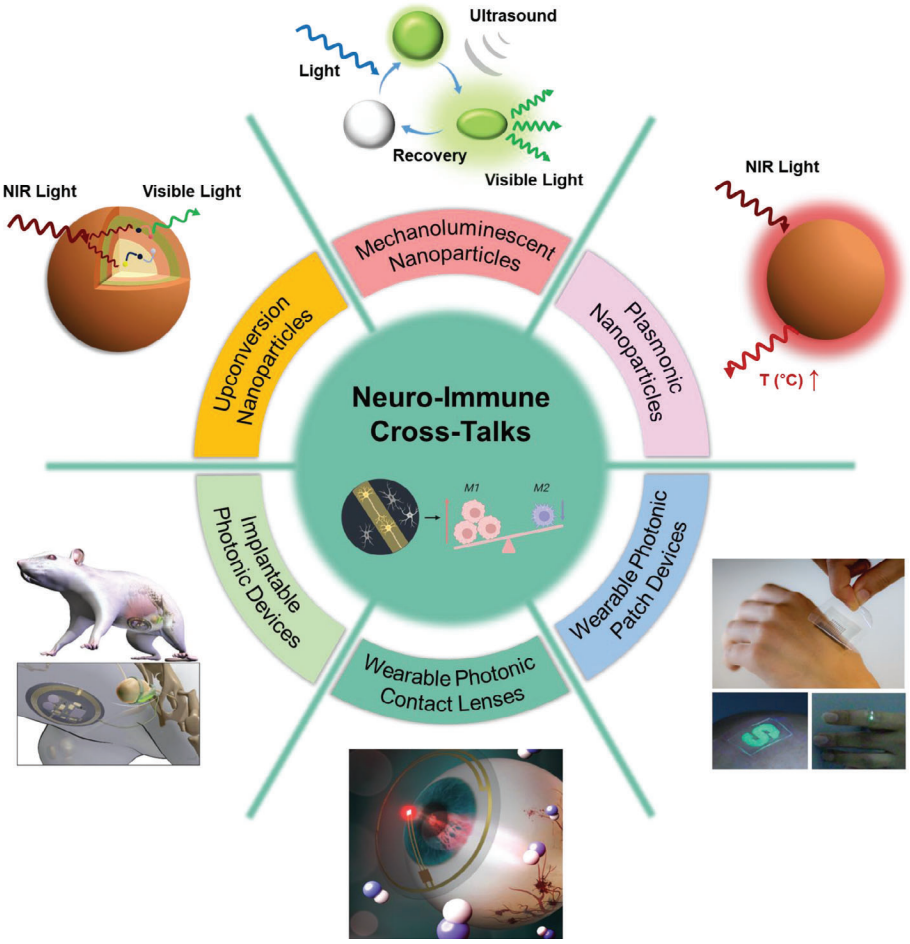


Figure 10. The schematic perspective of multifunctional photonic nanomaterials and devices for digital photomedicine via neuro-immune cross-talks.

and implantable photonic devices, along with innovative photonic nanomaterials, holds significant potential for revolutionizing the treatment of neurological and immune-related disorders. While challenges remain, particularly with neuro-immune interactions and translation, the progress outlined in this *Perspective* suggests a future where precisely targeted therapies can be realized with minimal negative side effects. Continuous interdisciplinary research would be essential to fully harness the therapeutic potential of these emerging technologies, ultimately leading to more effective and personalized treatments for complicated diseases. Here, we highlight the potential research directions from the perspectives of photonic nanomaterials and devices for futuristic digital photomedicine via neuro-immune cross-talks as follows:

1) There have been several reports on notable strategies to significantly improve the brightness and efficiency of UCNPs for deep tissue imaging and therapeutic applications. The enhancement of UCNP luminescence efficiency is based on advanced surface engineering techniques, such as coating UCNPs with additional materials to boost energy transfer and minimize non-radiative loss.[214,215] In addition, the ultrasound-driven recharging mechanisms and the hybrid systems of MLNPs and other nanoparticles would ensure continuous activation and energy transfer,[216,217] addressing the recharging limitation. In addition, artificial intelligence (AI) can be used for the design, optimization, and real-time monitoring of nanomaterials in diagnosing diseases by the analysis of medical imaging.[34,218] Deep learning algorithms, in particular, have demonstrated high accuracy in detecting conditions like cancer and cardiovascular diseases from X-rays, MRIs, and CT scans. These models can efficiently handle large data sets, often performing at or above the level of human experts in some areas.
2) Multidisciplinary research is advancing toward smart lenses capable of not only delivering therapeutic light but also responding to specific physiological signals by releasing drugs directly to affected areas such as the retina or brain.[219,220] This dual functionality would enhance therapeutic outcomes in various diseases like Alzheimer's, Parkinson's, glaucoma, and diabetic retinopathy by providing both immediate neuromodulation and sustained drug release tailored to the patient's needs. Moreover, adaptive smart photonic lenses equipped with real-time sensors to monitor physiological parameters like intraocular pressure or neural activity would enable dynamic adjustments in light intensity and drug dosage, optimizing the treatment efficiency with minimized side effects.[221,222] These advancements would transform

these smart lenses into multifunctional therapeutic platforms to manage chronic diseases by controlling intraocular pressure, reducing inflammation, and promoting healing, potentially providing systemic treatments via the optic nerve or blood-retina barrier.

3) The advanced 3D optoelectronic systems are wirelessly integrated for precise, efficient, and non-invasive neurostimulation and physiological monitoring.[184,223,224] These systems aim to maintain close and consistent contact with complex organ surfaces,[183] overcoming challenges posed by biofluids and gaps that can reduce the stimulation efficiency. By utilizing stretchable, lithographically defined membranes that conform to the natural shapes of organs, these devices enable robust and accurate data collection and stimulation, particularly in dynamic environments such as the heart. Furthermore, the integration of wireless power transfer systems, which eliminate the need for bulky batteries and reduce infection risks, represents a significant leap forward.[225] These wireless systems are designed for high energy efficiency and minimal thermal effects, ensuring safe and effective operation even in complicated physiological conditions.[186,226] The combination of advanced materials, mechanical engineering, and cutting-edge wireless technology creates multifunctional platforms that can support a range of sensors and deliver tailored optical stimulations.[38,177] This comprehensive approach promises to revolutionize the fields of neurostimulation and immune regulation, providing new avenues for both research and further clinical applications.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

S.-J.K. and T.Y.K. contributed equally to this work. S.K.H. conceived the idea, supervised the project, and wrote the manuscript. S.-J.K. conceived the idea and wrote the manuscript on photonic nanomaterials and wearable devices. J.K. and H.K. wrote the manuscript on neuro-immune crosstalks. J.R. and T.Y.K. wrote the manuscript on implantable optogenetic devices. All authors contributed to the critical reading and revision of this manuscript.

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immune regulation, neurostimulation, optogenetics, photobiomodulation, photomedicine, photonic nanomaterials

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