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Enabling Biodegradable Functional Biomaterials for the Management of Neurological Disorders

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Abstract

An increasing number of patients are being diagnosed with neurological diseases, but are rarely cured because of the lack of curative therapeutic approaches. This situation creates an urgent clinical need to develop effective diagnosis and treatment strategies for repair and regeneration of injured or diseased neural tissues. In this regard, biodegradable functional biomaterials provide promising solutions to meet this demand owing to their unique responsiveness to external stimulation fields, which enable neuro-imaging, neuro-sensing, specific targeting, hyperthermia treatment, controlled drug delivery, and nerve regeneration. This review discusses recent progress in the research and development of biodegradable functional biomaterials including electroactive biomaterials, magnetic materials and photoactive biomaterials for the management of neurological disorders with emphasis on their applications in bioimaging (photoacoustic imaging, MRI and fluorescence imaging), biosensing (electrochemical sensing, magnetic sensing and opical sensing), and therapy strategies (drug delivery, hyperthermia treatment, and tissue engineering). It is expected that this review will provide an insightful discussion on the roles of biodegradable functional biomaterials in the diagnosis and treatment of neurological diseases, and lead to innovations for the design and development of the next generation biodegradable functional biomaterials.

Graphical abstract

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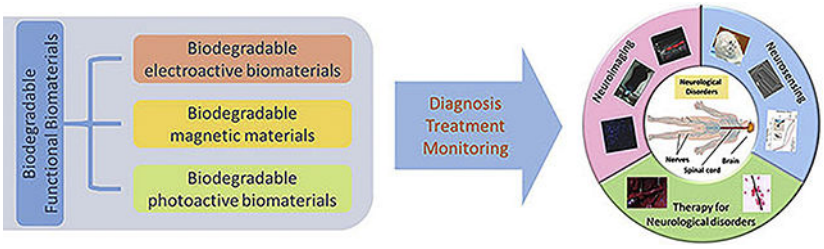
Conflict of Interest

J.Y. and The Pennsylvania State University have a financial interest in Acuitive Technologies, Inc. and Aleo BME, Inc. These interests have been reviewed by the University's Institutional and Individual Conflict of Interest Committees and are currently being managed by the University.



Keywords

neurological disorders; functional biomaterials; degradation; bioimaging; biosensing

1 Introduction

Neurological disorders are diseases of brain, spine and nerves that connect them. There are more than 600 diseases of the nervous system, such as Alzheimer’s disease, Parkinson's disease, traumatic brain injuries, brain tumors, epilepsy, and stroke, as well as less familiar ones such as frontotemporal dementia [1, 2]. The number of diagnosed refractory neurological diseases has been growing every year. According to the report by U.S. Pharmacist (Jan 2018), 20 million Americans experience neuropathy, and 16% of U.S. households have an individual with brain impairment. Each year, of the 1.2 million mostly diagnosed adult-onset brain disorders, 51.3% and 21% are caused by stroke and Alzheimer’s disease, respectively. Annually, the total number of newly diagnosed episodes of Parkinson’s disease and traumatic brain injury equals the total number of epilepsy episodes (135 million). As stated in the Central Brain Tumor Registry of the United States (CBTRUS) statistical report (2018), the overall estimated number of new cases of brain and other central nervous system (CNS) tumors in the U.S. for 2018 and 2019 are 85,440 and 86,970, respectively [3]. Many of these neurological diseases lack curative therapeutic approaches, causing the suffering and economic burden of patients. The challenges associated with the management of neurological disorders are numerous, including the poor understanding of the mechanism underlying the diseases, lack of the specificity in the diagnosis and treatment, the limited regenerative capability of adult neuron cells, especially in central nervous system (CNS), and the difficulty in drug administration across the blood brain barrier (BBB) effectively into brain [4-10].

The clinical need necessitates the development of innovative and effective diagnosis and treatment strategies for repair and regeneration of injured or diseased neurological tissues and organs. Recent progresses made in the bioimaging have enabled the detection of anatomical, biochemical and physiological conditions in different nervous systems, allowing a better understanding and more precise diagnosis of neurological diseases [11-16]. The bioimaging strategy can also provide post-treatment monitoring of neurological disorders to investigate treatment effects. In addition, advanced biosensing techniques that allow quantitative detection of neurotransmitters and biomarkers appears to be desired to improve the diagnosis and treatment process of neurological disorders [17-19]. As many neurological diseases are associated with changes of certain neurotransmitters and biomarkers in

biological fluid such as urine, plasma, serum and cerebrospinal fluids (CSF) [20-23]. Furthermore, the treatment for neurological disorders requires certain physical support to guide the growth and differentiation of nerve cells, as well as nanocarriers to facilitate the delivery of drugs, neuroprotective agents, and growth factors to across BBB and target to disease sites [8-10].

To fulfill the above mentioned demands for the diagnosis and treatment of neurological disorders, increasing efforts are being devoted to the development of advanced biomaterials [24]. Among all developed biomaterials, functional biomaterials including electroactive biomaterials, magnetic biomaterials and photoactive biomaterials are attracting more attentions. Nerve cells are intrinsically responsive to external stimulations such as electric field, magnetic field and light [25-28]. With the assistance of these functional biomaterials, external stimulations could be located to targeted nerve injuries. So the functional biomaterials can be popularly used as supporting scaffolds to guide nerve cell growth and tissue regeneration, especially under external stimulations [29]. In addition, with the latest evolution of nanobiotechnology, functional nanobiomaterials are developed and widely applied for neurological disease treatment. For instance, all the aforementioned three types of functional biomaterials can generate heat under external stimulation, so they are able to perform hyperthermia treatment and heat-triggered drug release [30, 31]. The electroactive biomaterials and magnetic biomaterials can also be precisely guided and collected in a specific location by an external electric field and magnetic field, respectively, enabling the potential to guide drugs to cross BBB and reach targeting disease sites [32]. Moreover, these functional biomaterials could work as imaging contrast agents, allowing photoacoustic imaging (electroactive biomaterials) [33], magnetic resonance imaging (MRI) (magnetic biomaterials) [34], and fluorescence imaging (photoactive biomaterials) [35] to facilitate precise diagnosis and efficient therapy for neurological disorders. Despite of all these advantages described above, most functional biomaterials are claimed to be biocompatible but usually are not biodegradable, which may cause chronic inflammation and need for surgical removal. Recently, an increasing number of studies have been conducted on the development of biodegradable functional biomaterials for the bioimaging [36-39], biosensing [40], and treatment of neurological disease [36, 41, 42]. In this manuscript, we focus on the roles of advanced biodegradable functional biomaterials including electroactive biomaterials, magnetic biomaterials and photoactive biomaterials in the understanding and treatment of neurological disorders. We particularly highlight their capabilities in bioimaging, biosensing and therapy strategies of neurological diseases.

2 Neurological Disorders

2.1 Nervous system and major disorders of the nervous system

The nervous system is the most complex and essential system in humans, and controls the sensory input, information integration, and motor output of the entire body. It is divided into two main parts: the central nervous system (CNS) consisting of the brain and spinal cord, which integrates and processes the information sent by nerves; and the peripheral nervous system (PNS) consisting mainly of nerves, which are enclosed bundles of long fibers, that carry sensory messages to the central nervous system (sensory nerves) and send commands

from the CNS to every other part of the body (motor nerves). At the cellular level, the nervous system is composed of two main types of cells: neurons and their supporting cells known as glial cells. As the structural and functional building blocks of the nervous system, neurons are organized and grouped into nerve bundles surrounded by protective connective tissues called myelin sheath, to conduct electrochemical signals rapidly and precisely via nerve impulse, and to release neurotransmitters (e.g. acetylcholine, dopamine and glutamate) that regulate the activation of muscles and glands via synapse. In addition, various types of glial cells (e.g. oligodentrocyts, astrocytes, ependymal cells, and microglia in CNS; Schwann cells and satellite cells in PNS) are present in the nervous system to protect and nourish the neurons.

Neurological disorders refer to any disorder of the nervous system, that is, any structural, biochemical or electrochemical abnormalities in the brain, spinal cord or other peripheral nerves that result in a range of severe symptoms with high mortality, morbidity and disability, representing a major public health problem [2]. There is a long list of neurological disorders, which can be classified according to the primary location affected, such as brain disorder, spinal cord disorder and peripheral neuropathy, or according to the primary type of dysfunction, such as structural disorder (e.g. traumatic injuries and brain tumor), biochemical disorder (e.g. Parkinson's disease) and electrochemical disorder (e.g. epilepsy seizure). Among over 600 different kinds of neurological diseases, we focus on the most common and costly neurological diseases, including traumatic brain injuries [43-47], brain tumor [48-51], Alzheimer's disease [5, 52-55], Parkinson's disease [4, 52], epilepsy [56-57], and stroke [58-60], which represent significant societal burden with parallel broad unmet needs of management.

2.2 Challenges and opportunities in the management of neurological disorders

The challenges associated with the management of neurological disorders are numerous, including the poor understanding of the mechanism underlying the diseases, lack of the specificity in the diagnosis and treatment, the limited regenerative capability of adult neuron cells, especially in CNS, and the difficulty in drug administration across the BBB effectively into brain.

First, the most significant success of disease management is expected to be based on a detailed understanding of the mechanism and the pathological molecular details of neurological diseases [10]. Unfortunately, the fundamental mechanism for most of the neurological disorders, particularly for neurodegenerative diseases, remains as undetermined due to their intrinsic complexity and heterogeneity [4, 5]. As a result, early diagnosis of neurological diseases is still lack of high specificity, and treatments up to now are merely symptomatic, leading to the fact that most neurological diseases are still not curable [10]. Fortunately, advances in molecular biology, genomics and proteomics are increasing and refreshing our understanding of the diseases, providing opportunity to uncover the underlying pathology and to identify disease-specific biomarkers. At the same time, although the traumas to the CNS arise from different forms and even from unknown reasons, there is a growing agreement that the injury processes share numerous key molecular mechanisms [44], such as the release of excitatory transmitters glutamate, calcium influx

into cells, mitochondrial dysfunction, free radical formation, cell apoptosis and the inflammatory reaction. Currently, there are well-defined molecular targets of neuroprotection, such as anti-inflammation therapy [9], anti-oxidant treatment, and anti-apoptotic agents [61]. However, to improve the accuracy of diagnosis and treatment effect of neurological diseases, more advanced bioimaging and biosensing technologies are desired to unfold the structure complexity and pathological molecular details of nervous system.

Additionally, the regeneration and reconstruction of nerve network remain as a challenge, especially for the CNS. The neurons in CNS have poorer self-healing capability compared with those in PNS, especially when additional structural (e.g. glial scars) and chemical obstructions (e.g. myelin-associated inhibitors [6]) in CNS have been found to further lower their intrinsic nerve regrowth potential [7]. Therefore, stem cell based therapy has received numerous attention to promote nerve regeneration, either by replacing the damaged or lost nerve cells, or by modulating the injury microenvironment through paracrine signaling to encourage endogenous repairing [62]. However, a few issues, such as tracking of stem cell migration and their survival, directional and controlled differentiation of the delivered stem cells, as well as physical support to guide transplanted stem cells and newly regenerated nerve cells, remain as unsolved to greatly slow down the translation of stem cell therapy.

Lastly, BBB acting as the barrier protecting the brain, not only blocks the bloodborne pathogens but also prevents most therapeutic drugs, neuroprotective agents and growth factors from entering the brain. Therefore, the design of powerful nanoparticles, which can deliver drugs, gene and small molecules (chemical stimulus or inhibitors) across BBB with minimal disruption to its structure and function, is a major objective for the treatments of a wide range of neurological disorders [8-10]. Despite the progresses, more advanced strategies and technologies are still required for the nanoparticle design to endow high targeting specificity, controlled releasing, and intracranial imaging-guided therapy.

To alleviate challenges mentioned above, a wide variety of biomaterials have offered great opportunities for diagnosis and treatment of neurological disorders, including nanoparticles for neuro-imaging and neuro-sensing, scaffolds for promoting nerve regeneration, systems for promoting stem-cell-mediated therapy, nanocarriers for enabling BBB crossing of drugs or gene. Among all applied biomaterials, biodegradable functional biomaterials including biodegradable electroactive biomaterials, biodegradable magnetic biomaterials and biodegradable photoactive biomaterials are attracting more attentions. The biodegradable functional biomaterials are superior to regular biomaterials because they are intrinsically responsive to external stimulation fields like electric field, magnetic field and light. This special property of biodegradable functional biomaterials provide them with improved interactions with nerve cells, higher targeting accuracy, and better imaging capability than regular biomaterials. More detailed and specific discussions will be introduced in the following section.

3 Biodegradable functional biomaterials

The functional biomaterials we discuss in this review paper are focusing on electroactive biomaterials, magnetic biomaterials and photoactive biomaterials. These functional

biomaterials usually response to external stimulations from electric field, magnetic field and light, which in turn could adjust their interactions with nerve cells to modulate cellular activities. Functional biomaterials also have the ability to interact with neurotransmitters and biomarkers, enabling neuro-sensing that increases diagnosis accuracy. In addition, the functional biomaterials are able to generate heat under external stimulation fields, allowing heat-triggered controlled release and hyperthermia treatment. With the help of external fields, functional biomaterials can also be guided to a targeted location, enabling the delivery of functional agents to pass through BBB and reach disease sites. Furthermore, these functional biomaterials possess intrinsic imaging capability, including photoacoustic imaging (electroactive biomaterials), magnetic resonance imaging (MRI) (magnetic biomaterials), and fluorescence imaging (photoactive biomaterials), providing noninvasive neuro-imaging to facilitate diagnosis and treatment of neurological disorders. In addition to all these advantages of functional biomaterials for neurological disorders, biodegradable functional biomaterials possess extra benefits. The applied biodegradable functional biomaterials can be degraded *in vivo,* and then absorbed by or removed from human body after finishing their usage, which strongly eliminates the concern of chronic inflammation and the need for surgical removal of implants. The cytocompatibility and biocompatibility of biodegradable functional biomaterials have been widely proved. For example, Guo et al. reported that many biodegradable conductive polymers were verified with cytocompatibility in cell culturing studies with nerve cell lines such as PC12 cells and Schwann cells [63]. Studies also demonstrated magnetic poly(lactic acid) (PLA)-SPION nanocomposites with high levels of encapsulated magnetite achieve efficient labeling (≥90%) of primary neural stem cells without significant toxicity [64]. In addition, biodegradable photoactive biomaterials such as a group of citrate-based BPLPs have been confirmed with excellent biocompatibility through both *in vitro* cytocompatibility and *in vivo* foreign body response studies [65]. Therefore, the studies conducted on biodegradable functional biomaterials for the imaging, sensing, and treatment of neurological disease are increasing. In this section, we discuss the mechanisms, properties and functionalities of biodegradable functional biomaterials that utilized in the field of neurological disorders. Detailed applications in neuro-imaging, neuro-sensing and treatment of neurological diseases will be summarized in following sections.

3.1 Biodegradable electroactive biomaterials

Existing studies show that living organisms are complex electrochemical systems where each cell generates cell-type specific membrane potential producing endogenous electric fields throughout the biological system. The typical value of the potential is usually between −60mV and −100Mv [66]. Endogenous electric fields in the human body play an integral role in maintaining biological functions, such as muscle contraction, neural signaling, wound healing, embryogenesis, and tissue regeneration [67]. Endogenous electric fields (5–18 mV/mm) was observed to polarize the nerve system along the rostral–caudal axis and guide nerve cell growth [25]. In addition, major activities of nerve cells are usually accompanied by electrical changes. For instance, when the signaling process of the nerve system is active, the transmembrane potential changes from negative to positive [66]. Regarding the electrical properties of nerve cells, exogenous electrical stimulation strongly affects their activities. Initial studies investigating the effect of electrical stimulation on

nerve cells were conducted on *Xenopus* neurons by exposing them to electric fields from 0.1 to 10 V/cm, proving that electric fields were able to influence the orientation and length of neurite growth [25]. Later, Wood *et al.* also demonstrated that the application of a 25 V/m DC electrical stimulation for 10 min enhanced overall neurite outgrowth over controls for up to 48 h [68]. Moreover, Yamada *et al.* reported that mild electrical stimulation could influences embryonic stem cells to differentiate into neuronal cells [69]. Several theories have been suggested to explain the mechanism of electrical stimulation on nerve cells. For instance, it was proposed that electrical stimulation alters protein synthesis in transected sciatic nerve segments and promotes neurite outgrowth. Kimura *et al.* suggested that electrical stimulation were able to electrically activate gene expression for nerve growth factor (NGF) for rat neuronal pheochromocytoma cells (PC12 cells) [66]. Recently, Chan *et al.* claimed that electrical stimulation boosts neuronal expression of neurotrophic factors and their receptors. The elevated neurotrophic factor levels cause an upregulation of cAMP level, enabling increased expression of nerve regeneration-associated genes such as tubulin, actin and GAP-43 [70].

Despite the advantages of direct exogenous electric fields for nerve stimulation, it's hard to be applied to targeted nerve tissues. In order to provide more precise control over stimulation conditions, electroactive polymers have become very important tools. Conductive polymers were first reported in 1977 when researchers developed the conductive polyacetylene [29]. Conductive polymers are a new generation of organic materials that characteristically have a conjugated backbone structure with a high degree of π-orbital overlap. The π-conjugated polymers in general are not conductive, and only turn to a conductive state after a doping process. Doping is the process of oxidizing (p-doping) or reducing (n-doping) the neutral conjugated polymer and providing a counter anion or cation, respectively. In this process, charge carriers, in the form of charged polarons and bipolarons, are introduced into the polymer chain. Ordered movement of these charge carriers along the conjugated backbone generates electrical conductivity. Conductive polymers possess similar electrical and optical properties to those of metals and inorganic semiconductors, but have better processability, designability and biocompatibility. Based on their electroactivity and strong light absorption, conductive polymers have been greatly investigated for modulation of cellular activities, controllably release of drugs and biological molecules [71], detection of neurotransmitters and biochemical reactions [72], as well as photoacoustic imaging [73]. Various conductive polymers, such as polyaniline (PANI) [74], polypyrrole (PPy) [75], and poly(3,4-ethylene dioxythiophene) (PEDOT) [76], have been investigated for alleviating neurological disorders and nerve regeneration.

One of the greatest drawbacks of conductive polymers for *in vivo* applications is their inherent inability to degrade, which may cause chronic inflammation and need for surgical removal [63]. To address this limitation, attempts to develop biodegradable conductive polymers have been carried out. One applied strategy is making polymer blends or composites with conductive polymers and biodegradable polymers. For instance, nerve conduits were fabricated with the composite of PPy and poly (D,L-lactic acid) (PDLLA) to facilitate nerve defect regeneration. The obtained PPY/PDLLA composite nerve conduits were proved to support the differentiation of rat pheochromocytoma 12 (PC12) cells under electrical stimulation *in vitro* and promote nerve regeneration for a rat sciatic nerve defect

[41]. Another widely studied method for preparing biodegradable conductive polymers is to develop copolymers with conductive oligomers and biodegradable polymers. Wu *et al.* developed a biodegradable conductive polyurethane by polycondensation of poly(glycerol sebacate) and aniline pentamer, which significantly enhanced Schwann cells' myelin gene expression and neurotrophin secretion for peripheral nerve tissue regeneration [77], Recently, biodegradable conductive polymers are greatly replacing traditional non-degradable conductive polymers in the field of neurological disorders, including neuro-imaging, neurosensing, and treatment.

3.2 Biodegradable magnetic biomaterials

Magnetism is an intrinsic property of every atom. Substantial evidences have shown that all living organisms contain magnetic particles and can act as magnetic receptors [26]. Magnetotactic bacteria, a phylogenetically diverse group of aquatic bacteria, are perhaps the first living organisms to orient themselves with the earth's magnetic field [78]. These bacteria align along magnetic fields with the help of a chain of organelles containing magnetosomes, and swim along the field lines with the help of their flagella. The magnetosomes are magnetic nanoparticles such as magnetite (Fe_3O_4) and greigite (Fe_3S_4). The haemoglobin in our blood is an iron (Fe) containing protein. In the 1930s, haemoglobin was found with magnetic properties that differed depending on whether oxygen was carried. The haemoglobin carrying no oxygen was found to be more sensitive to magnetic field than oxygenated blood [79]. These results established that the magnetic field and magnetic materials have a significant role to play in healthcare and biological applications. In particular, much effort has been devoted to the design and synthesis of magnetic nanoparticles, due to their multifunctional properties including small size, high operational surface areas, and unusual superparamagnetic behavior. Magnetic nanoparticles are typically classified into pure metals (Fe, Co, Ti, Ni, etc.), metal oxides (Fe_3O_4, maghemite (γ-Fe_2O_3), etc.), ferrites ($BaFe_{12}O_{19}$, $SrFe_{12}O_{19}$, $CuFe_2O_4$, $NiFe_2O_4$, $MnFe_2O_4$, etc.), and metal alloys (CoPt, FePt, etc.) [30, 80]. Among all magnetic nanoparticles, iron oxide nanoparticles, typically Fe_3O_4 and γ-Fe_2O_3, have been most extensively studied and applied in biomedicine due to their low toxicity [81]. Magnetic iron oxide nanoparticles exhibit fast change of magnetic state under an external magnetic field (high magnetic susceptibility) and loss of magnetization after removal of the magnetic field (superparamagnetism) are usually desired for biomedical applications. In order to achieve superparamagnetism, magnetic iron oxide nanoparticles typically with sizes below 20 nm, and are named superparamagnetic iron oxide nanoparticles (SPIONs) [82, 83]. However, particle sizes should not be too small (< 10 nm). Otherwise, they would have rapid renal clearance and low values of saturation magnetization (SM). SM represents the maximum level of achievable magnetization of SPIONs under an external magnetic field, and it also determines their capability of producing heat [84].

The appropriate functionalization of the SPIONs for biomedical applications is ruled not only by their intrinsic magnetic properties but also by their biophysical properties. Modifications with biomolecules, targeting agents, and biocompatible materials are suggested to enable SPIONs with required biocompatibility, targeting specificity, pharmacokinetics, biodistribution, and cell interaction processes [85, 86]. For example, the

surface modification of biocompatible polymers renders SPIONs with multiple advantages such as longer circulation time, better protection of drugs, and less undesired accumulation in important organs to improve drug delivery efficiency. It was reported that polyethylene glycol (PEG) functionalized SPIONs demonstrated double the amount of circulation time and reduced nanoparticle accumulation in untargeted organs [87]. In order to develop biodegradable magnetic materials, SPIONs have been incorporated with biodegradable polymers through various strategies including surface coating, encapsulation, and chemical conjugation.

With the latest evolution of nanobiotechnology and biomaterials, biodegradable magnetic materials are attracting increasing attention due to their potential to improve conventional diagnostic and therapeutic procedures. Due to their superparamagnetism, biodegradable magnetic nanoparticles can be precisely guided and collected in a desired location by an external magnetic field [32]. In order to realize specific and controlled drug delivery, the drug molecules can be connected to the nanoparticles through a cleavable linker or encapsulation. Once they reach the target site under the external magnetic field, drugs can be released locally either via enzymatic cleavage or changes in the physiological environment. For instance, pH triggered nanoparticle drug release system was developed by a biodegradable poly(ethylene glycol)-*b*-poly(2-[diisopropylamino]ethyl aspartate) block copolymer loaded with doxorubicin and SPIONs. Once the magnetic nanoparticles reached acidic microenvironment of tumors, the drug release rate was approximately ten-times higher than that in a neutral environment [88]. Moreover, SPIO nanoparticles are being developed for hyperthermia treatment and heat-triggered drug release as a result of their ability to convert magnetic energy into heat [30]. Kim *et al.* used a multifunctional thermo-responsive poly(N-isopropylacrylamide-co-acrylamide)-block-poly(ε-caprolactone) (P(NIPAAm-*co*-AAm)-*b*-PCL) copolymer to encapsulate doxorubicin and SPIONs, and fabricated a magnetic hyperthermia-mediated payload release micelle system. Taking advantage of the magnetic hyperthermia of SPIONs and thermal sensitivity of the polymer, the nanoparticles were able to release drugs under the regulation of external magnetic field [89]. Also, biodegradable magnetic materials exhibit synergic effect on cell adhesion, proliferation, and differentiation, so they have also been investigated for tissue engineering applications. Wei *et al.* developed biodegradable magnetic nanofibrous membranes by electrospinning of Fe_3O_4/chitosan (CS)/poly vinyl alcohol (PVA), which significantly promoted the adhesion and proliferation of MG63 cells [90]. It is well known that biodegradable magnetic materials can be used as magnetic resonance imaging (MRI) contrast agents for bioimaging purpose. The imaging performance is affected by many conditions including the strength of applied magnetic field, the acquisition time, the SM of the nanoparticles, and concentration of the nanoparticles. A water-dispersible and tumor-targeted MRI contrast agent was manufactured through encapsulation of nonclustered SPIONs with folate modified copolymers of poly(ethylene glycol) and poly(ε-caprolactone) (Fa-PEG-PCL). The resulting small-sized (35 nm) nanomicelles (Fa–PEG4.3k–PCL1k–SPION) displayed efficient MRI effect within the tumor section [91]. Regarding the multifunctionality of biodegradable magnetic materials, Ye *et al.* developed biodegradable poly(lactic-co-glycolic acid) (PLGA) vesicles containing magnetic nanoparticles, quantum dots (QDs) and anticancer drugs as a nanocarrier system for both bioimaging and anticancer

drug delivery [92]. Therefore, biodegradable magnetic materials can serve as a multifunctional system to simultaneously provide specific targeting, drug administration, tissue regeneration, and *in vivo* real-time therapeutic response monitoring, enabling the potential for precise personalized medical care applications [93].

3.3 Biodegradable photoactive biomaterials

Light is readily modulated in space, time, and intensity, providing an inexpensive and specific tool for mediating biological behaviors of various cells such as nerve cells, muscle cells, stem cells, and macrophage. The infrared neural stimulation (INS) has been shown to induce both excitation and inhibition of neural activity depending on the stimulation condition [27, 28]. Effective INS was demonstrated on CNS [94] and PNS [95]. enabling more understanding and better theranostic strategies for neurological diseases. Wang *et al.* investigated light stimulation effects with different lights on human adipose derived stem cells (hASCs). One of their studies demonstrated that blue (415 nm) and green (540 nm) wavelengths were more effective in stimulating osteoblast differentiation of hASCs than red (660 nm) and (NIR (810 nm) lights, because blue/green lights produced a bigger increase in intracellular calcium and reactive oxygen species (ROS). In another study, they found that blue/green lights inhibit the proliferation of hASCs, while red/NIR lights stimulates the process. The reason is that blue/green wavelengths decrease cellular ATP, while red/NIR increase ATP in a biphasic manner [96]. Kang *et al.* also reported the ability of NIR light to regulate intracellular calcium in order to modulate macrophage polarization [97]. Among all the probable mechanisms of light stimulation effects, including electric field mediation, photo-mechanical transform and photo-thermal transform, the most likely appears to be photo-thermal transform [98, 99]. The absorption of light pulse by the tissue's water causes a rapid local increase in temperature. This heating alters the electrical capacitance of plasma membrane, depolarizing the target cells. This mechanism is reversible and broadly applicable to most cell membranes [100]. In addition, optogenetics is a technique whereby light-responsive ion channels are introduced into target cells, enabling unprecedented precision and specificity for neuron modulation. This technology has even been involved in the treatment of diseases such as Parkinson's disease, hereditary blindness, and epilepsy with chronic light stimulation [101-103].

Regarding the significant role of light regulation played in neurobiology, photoactive biomaterials are becoming promising tools due to their capability of photo-thermal conversion, fluorescence and light guidance. In the following sections, photoactive biomaterials and related devices, including photothermal biomaterials, fluorescent biomaterials and optical waveguides, will be outlined, discussing their material design, properties and possible applications.

Photothermal materials are a family of photoactive materials that release thermal energy after light radiation. The thermal energy can be used to change material properties to release chemicals and drugs, stimulate surrounding cells, and kill cancer cells. Conductive and semiconductive polymers are among the most popular photothermal biomaterials for biomedical applications. Li *et al.* demonstrated that PPY microgels could be used for light-controlled release of neurotransmitters when triggered by NIR irradiation [31].

Nanoparticles made by a NIR-excited semiconducting copolymer, poly(cyclopentadithiophene-*alt*-diketopyrrolopyrrole), were reported to be able to control thermosensitive ion channels in neurons, instigating neuron depolarization [104]. Another semiconductive polymer poly(3-hexylthiophene-2,5-diyl) (P3HT) also demonstrated great photothermal effect, which has been utilized to regulate membrane hyperpolarization of hippocampal neurons and human embryonic kidney (HEK-293) cells [28, 105]. In addition to conductive and semiconductive polymers, magnetic nanoparticles are another kind of widely used photothermal biomaterials. Chu *et al.* investigated the hyperthermia treatment effect for esophageal cancer by Fe_3O_4 nanoparticles coated with carboxyl-terminated poly (ethylene glycol)-phospholipid. It was found that the surface-functionalized Fe_3O_4 nanoparticles had no obvious toxicity to esophageal cancer cells without NIR irradiation, but presented effective suppression on *in vitro* cell viability and significant inhibition on *in vivo* tumor growth with NIR irradiation [106]. Chen et al. also demonstrated that the highly crystallized iron oxide nanoparticles (HCIONPs) coated with a polysiloxane-containing copolymer could be used as effective and biodegradable mediators for photothermal therapy of SUM-159 breast cancer [107].

Fluorescent materials are a special group of photoactive materials. A large amount of biocompatible and biodegradable fluorescent materials have attracted significant attentions in biomedical fields of theranostic and regenerative medicine [108]. Most reported biodegradable fluorescent materials are made through the encapsulation or conjugation of fluorescent organic dyes [109] or inorganic QDs [110, 111] with biodegradable polymers. However, the photobleaching of organic dyes and toxicity of QDs have largely limited their *in vivo* applications and motivated the design of fully biodegradable and biocompatible fluorescent materials. Benefitting from the reactive nature of citric acid, Yang's lab developed a series of citrate-based biodegradable polymers through a convenient and cost-effective thermal polycondensation reaction of citric acid and biocompatible diols [112-116], Among the citrate-based biomaterials, a group of biodegradable photoluminescent polymers (BPLPs) were created by introducing amino acids to the system [114, 117-121]. In the reaction, citric acid and amino acids contributed to both the formation of molecular fluorophores and development of the polymer backbones, while the diol is mainly responsible for the construction of polymer backbones. The distinctive fluorescence properties of BPLPs were tunable by changing amino acids, monomer feeding ratios and even excitation wavelengths [119]. Among all kinds of BPLPs, BPLP-Cys (using L-cysteine) displayed excitation-independent fluorescence with a strong emission (~ 430 nm) and h a high quantum yield of 62.3%. It also possessed a high photostability with photobleaching of about 2% after 3h of continuous UV excitation, while the traditional organic dye rhodamine-B had about 10% photobleaching under the same excitation condition. BPLP-Ser (using L-serine), which had a QY of 26.0%, was an exemplified BPLP that showed an excitation-dependent emission from blue to red and even NIR by increasing excitation from 310 to 573 nm. This unique fluorescence property not only allows BPLP-Ser to be a promising material for deep tissue imaging, but also gives it potential for multiplex optical imaging. In addition to their fluorescence properties, BPLPs demonstrated high designability due to their reactive side groups (carboxyl group, hydroxyl group, and amino group). These reactive groups have facilitated BPLPs to be modified with different chemical

structures, physical properties, and biological functionalities, enabling a wide variety of applications including biological labeling and imaging [122, 123], biosensing [124], drug delivery [123, 125-127], and regenerative medicine [119, 122, 125]. Recently, by doping BPLP-Cys with conductive aniline tetramer, a citrate-based fluorescence/photoacoustic dual-imaging enabled biodegradable polymer (BPLPAT) has been developed. The BPLPAT nanoparticles were applied for label PC12 nerve cells and performing deep tissue detection [36].

Due to significant scattering and absorption loss, light cannot be efficaciously delivered to or collected from target regions within deep tissue, significantly hindering the execution of *in vivo* light stimulation. A traditional strategy is to apply long wavelength NIR or infrared radiation to provide a relatively deep penetration up to about a couple cm, which is still insufficient for full body applications [128]. Another effective method for alleviating this problem is implanting optical waveguide in tissues or organs for light delivery. To date, silica glass remains the mainstream optical material platform because of their capability to achieve efficient light delivery with low loss [129]. However, silica fibers often suffer from mechanical fragility and brittleness, limited biological functionalities, as well as nondegradability, hindering their application as implantable devices. Benefiting from the recent progress of polymeric biomaterials, many optical waveguides with high optical efficiency and flexible mechanics have been developed with advanced polymeric biomaterials, including bacteria cell-based biomaterials [130, 131, naturally derived biomaterials [132-134], and synthetic biomaterials [135, 136]. Among the optical waveguides, those made from synthetic biodegradable polymer are more attractive candidates due to their excellent biocompatibility, programmable degradation, adjustable mechanics, and flexible designability [137]. For instance, Shan *et al.* reported a biocompatible and biodegradable step-index optical fiber fabricated from citrate-based polymeric elastomers. The designability and processability of citrate-based biomaterials enable ultra-fine tuning of refractive index difference between the core and the cladding layers, while maintain homogenous biodegradation rate and identical mechanical properties to yield high device integrity. A 0.4 dB/cm loss allows the flexible optical fiber to perform efficient image transmission and *in vivo* deep tissue optical imaging [136]. Fu *et al.* also developed biodegradable PLLA fibers with high mechanical flexibility and optical transparency using a thermal drawing process. The fibers were implemented *in vivo* as optical neural interfaces for intracranial light delivery and detection, allowing deep brain fluorescence sensing and optogenetic interrogation [38].

4 Biodegradable functional biomaterials for neuro-imaging

Neurological disorders that combine cognitive, motor, and behavior abnormalities are often mistakenly diagnosed as diseases such as depression, motor impairments, and lethargy that follow debilitating immune suppression [138]. A better understanding of their symptom and pathology is desired to facilitate precise diagnosis of the diseases at early stages before overt symptoms. Recent progresses made in bioimaging have enabled the detection of anatomical, biochemical and physiological conditions in nervous systems. Moreover, the bioimaging strategy can also provide post-treatment monitoring of neurological disorders to investigate treatment effects [11]. Many of the well-established techniques such as photoacoustic

imaging, MRI, optical imaging, positron emission tomography (PET), single photon emission tomography (SPECT), and computer tomography (CT) have gained considerable interest and applicability in neurological diagnostic studies. In order to increase the precision and practicality of neuro-imaging, various biocompatible and biodegradable materials have been used as contrast agents and carriers of contrast agents in the imaging process. In the following sections, imaging modalities that involve biodegradable functional biomaterials will be discussed.

4.1 Photoacoustic imaging for neurological disorders

Photoacoustic imaging is a hybrid imaging modality that combines optical image contrast and ultrasound detection principles [139, 140]. Illuminated by non-ionizing laser pulses, targeted subjects absorb the light and convert it into heat, leading to transient thermoelastic expansion and thus wideband ultrasonic acoustic signal. The generated ultrasonic waves are then detected by transducers to form images. Photoacoustic imaging can overcome this primary challenge of shallow penetration of optical techniques because of the lower ultrasonic scattering coefficients of absorbents compared with their optical equivalents, so the propagation of the photons in the diffuse regime enables photoacoustic imaging with a penetration depth up to ~50 mm with a resolution of <1 mm. Overall, photoacoustic imaging combines the good contrast and multiplexing capabilities of optical imaging and the deep penetration and 3D imaging capability of ultrasound imaging.

It has been widely used for neuro-imaging. The image contrast is primarily determined by the light absorption properties of the tissue, and the imaging frame rate is controlled by the sound speed in tissue (typically about 1.5 mm/μs) and the pulse repetition rate of laser (10 Hz to 5 kHz) [141]. There are some endogenous substances with special light absorption such as hemoglobin, melanin, and lipid, have been used as photoacoustic contrast agents [142]. In brain tissues, hemoglobin can be used as a photoacoustic contrast agent for label-free vascular imaging. As oxyhemoglobin and deoxyhemoglobin have different light absorption spectra, photoacoustic imaging is able to quantitatively measure the total hemoglobin concentration and oxygen saturation, which are difficult to be measured with many other neuroimaging modalities. In addition to endogenous contrast agents, exogenous contrast agents, such as nanoparticles [143], organic dyes [144], and fluorescence proteins [145], are used to further enhance the sensitivity, specificity and contrast of photoacoustic imaging, allowing for molecular neuro-imaging. For instance, conjugated polymer nanoparticles demonstrated highly efficient photoacoustic imaging of orthotopic brain tumors [12] and brain vascular imaging [146]. NIR dye (Prussian blue) labeled Mesenchymal Stem Cells also demonstrated successful photoacoustic imaging for the detection of brain injury and rehabilitation [13]. In order to relieve safety concerns for *in vivo* applications, biocompatible and/or biodegradable functional biomaterials have also been applied as exogenous photoacoustic contrast agents for neuro-imaging. Zha *et al.* developed a biocompatible conductive monodispersed PPy nanoparticles (~46 nm) with strong absorption in NIR range through a facile aqueous dispersion method. The PPy nanoparticles demonstrated great photoacoustic imaging ability with deep penetration (~4.3 cm under chicken breast muscle) and low background noise, allowing a better imaging efficiency than that of hemoglobin in blood. After intravenous administration, the polyvinyl

alcohol (PVA)-stabilized PPy nanoparticles exhibited clear brain vascular imaging of mouse [33]. Recently, a biodegradable conductive aniline tetramer doped citrate-based polymer with strong photoacoustic effect after excitation with NIR light was synthesized. Combined with its significant promotion of the proliferation and differentiation of nerve cells, the newly developed biodegradable conductive materials are a promising candidate for use in neuro-imaging and nerve regeneration [36].

4.2 MRI for neurological disorders

MRI is based on the relaxation process of water protons generated by a contrast agent in the presence of external electric field. When a proper radio frequency is applied and absorbed by the latters, it leads to spin flipping. Once the external electric field is removed, the proton spins relax. During the relaxation process, a weak radio frequency is generated and detected by the receiver coils, enabling the image creation by the equipment software [147, 148]. Contrast agents play an important role by enhancing the contrast and improving the sensitivity of MRI [149]. The relaxation process occurs in a longitudinal (T1) and a transverse (T2) plane and therefore contrast agents for MRI can be classified into T1 and T2 agents. The former are positive contrast agents, typically contain paramagnetic gadolinium (Gd) derivatives, to reduce proton longitudinal relaxation time (T1), thereby enhancing the MRI signal. Another are negative contrast agents, which are usually composed of superparamagnetic nanoparticles, for reducing the transverse relaxation time (T2) of surrounding water protons, thus decreasing signal intensity [150]. MRI can penetrate deep into tissues, and conduct non-invasive entire body imaging with relatively high spatial resolution (~50 μm) and sequential repeatability [151]. Various superparamagnetic nanoparticles and Gd derivatives based nanoparticles have been developed for molecular, cellular and tissue imaging applications [152-155].

As one of the most powerful techniques in modern clinical diagnostics, MRI has widely been involved as a great imaging tool during the diagnosis, therapy and post-treatment monitoring processes of neurological disorders including Parkinson's disease [156, 157], Alzheimer's disease [14], Wilson' s disease [158], stroke [159], brain tumors [160], and neuronal intranuclear inclusion disease [161]. For example, SPIONs have been utilized to detect amyloid plaques and Aβ plaques in Alzheimer's disease transgenic mice with MRI [34]. Stroh *et al.* also demonstrated a long term tracking of SPIONs labeled stem cells with MRI in a Rat Model of Parkinson disease, providing evaluation of stem cell-based therapies for the disease [156]. To improve the *in vivo* circulating time and biocompatibility of MRI contrast agents, biodegradable polymer encapsulated magnetic nanoparticles have been fabricated. Norman et al. developed wheat germ agglutinin coated magnetite nanoparticles, and used them for neural stem cell labeling [162]. Furthermore, Granot et al. prepared biodegradable magnetic PLGA nanoparticles (~100 nm) and microparticles (1-2 μm) for MRI-based cell tracking. The magnetic microparticles enabled *in vivo* imaging of the migration of endogenous neural progenitor cells in rat brain over 2 weeks, providing higher contrast to noise ratio than inert micron-sized iron oxide particles (Fig. 1A-C) [37].

4.3 Optical imaging for neurological disorders

Optical imaging is performed based on the interactions of lights (infrared (300 GHz-430 THz, 700 nm-1 mm), visible (430-790 THz, 380-700 nm), and ultraviolet light (790 THz-30 PHz, 10-300 nm)) with detecting objects [163]. Optical imaging techniques measure scattering, absorption, and luminescence of light that is either transmitted through or reflected out of objects. Light properties, both wavelength and intensity, determine the imaging penetration depth and size. Optical imaging provides high temporal resolution, but reduced spatial resolution with increased penetration depth. Also, it is often limited in penetration depths (< 1 cm), so traditional fluorescence imaging have been mostly confined to *in vitro* applications such as cell labeling, immunohistochemistry, and flow cytometry. However, recent development of fluorescent agents with longer excitation/emission wavelengths (e.g. near-infrared (NIR)) as well as advancement of biocompatible optical waveguides have allowed light to be delivered deeper into tissues, greatly improving the viability of optical imaging for *in vivo* applications [164-166].

Optical imaging has unique advantages associated with low cost, simplicity, and easy-to-operate equipment, offering a variety of interrogations from intrinsic functional information on blood oxygenation to molecular sensing [167]. As such, optical imaging is applied a useful tool for neuro-imaging. Neural stem cells-mediated therapy is emerging as a promising approach to treat a wide variety of neurological diseases [15, 16]. However, their clinical applications are severely constrained by challenges such as tracking the survival rate and migration of the stem cells, evaluating their “stemness” and directional differentiation, and monitoring their therapy effect [62, 168]. To address these challenges, Wang *et al.* developed an optical imaging system. In particular, they created biodegradable PLGA nanovehicles loaded with fluorescent 6-courmarin and retinoic acid (one of the most potent morphogens to induce stem cell differentiation into neuron subtypes) using a nanoprecipitation method, enabling real-time tracking of the differentiation dynamics of transplanted neural stem cells after traumatic brain injuries [35].

As an effective way to alleviate the light penetration problem of optical imaging, optical waveguides have also been utilized in the field of neuro-imaging to provide organ-scale light delivery and collection. For instance, Fu *et al.* developed implantable and biodegradable PLLA fibers that can be used for optical neural interfaces [38]. Specifically, the PLLA optical fiber was implanted into the hypothalamus, which had been stimulated with a high expression of enhanced green fluorescence protein (EGFP), of a freely moving mouse. Later, an excitation light (488 nm) from a laser source was delivered via the optical fiber into the hypothalamus. The green fluorescence from EGFP was able to be collected and guided by the same fiber, and then received by a standard detector. The detected fluorescence signals decrease with time, revealing the degradation of PLLA optical fibers *in vivo.* The same optical fiber was also used to demonstrate optogenetic interrogation *in vivo* (Fig. 1D-J).

4.4 Multimodality imaging for neurological disorders

The nervous system and the pathologies of neurological diseases are extremely complex. To allow better understanding of the system and more accurate diagnosis of neurological disorders, improved imaging strategies are desired to provide comprehensive and detailed

information of both healthy and diseased nervous systems. As such, an ideal neuro-imaging technique is expected to possess high temporal and spatial resolution, ability for histological and functional analysis, availability for long-term tracking, and high specificity to the targeted areas. However, each imaging modality has its own merits and limits, and there is no single imaging technique that fulfills all of the above conditions. Thus, the current mainstream approach is to combine multiple imaging modalities to achieve optimal imaging strategies. For instance, MRI is excellent for spatial resolution and soft-tissue contrast, but is far less sensitive than optical imaging. The integration of these two complementary imaging modalities would improve neuro-imaging effect. By incorporating Fe_3O_4 nanoparticles and Cy5.5-labled lactoferrin into pH/temperature sensitive nanogels, Jiang *et al.* developed a nano-system with both dual modality MR/fluorescence imaging capability and brain tumor (Glioma) targeting specificity. The resulting multifunctional nanogels demonstrated efficient MR/fluorescence imaging with high sensitivity and specificity for *in vivo* studies on rats bearing in situ glioma [169]. Another multimodal imaging study was conducted by Qiao et al. where MRI and photoacoustic imaging were combined for brain tumor imaging. The researchers developed gold-coated SPIONs (SPIO@Au), and used them to label bone marrow-derived human mesenchymal stem cells. Then the MSCs loaded with SPIO@Au were injected in mice bearing orthotopic U87 brain tumors via the carotid artery. Both MRI and photoacoustic imaging were applied for tracking the migration and distribution of MSCs in vivo, showing the possibility for real-time monitoring during stem cell-mediated therapy for brain tumors [170]. Furthermore, there were a few studies were conducted on biodegradable functional biomaterials that were able to perform multimodality neuro-imaging. Koffie et al. prepared biodegradable nanocarrier systems made of poly(n-butyl cyanoacrylate) dextran polymers coated with polysorbate 80 (PBCA nanoparticles). The BBB-impermeable fluorophores and MRI contrast agents labeled PBCA nanoparticles were allowed to cross the BBB into the brain for targeted molecular neuroimaging. Using the advanced PBCA nanocarrier system realized brain cellular imaging, *in vivo* visualization of amyloid plaques of Alzheimer's disease, as well as whole brain MRI [39]. Shan *et al.* also developed a citrate-based fluorescence/photoacoustic dual-imaging enabled biodegradable polymer (BPLPAT). The biodegradable dual-imaging BPLPAT nanoparticles were able to label PC12 nerve cells for fluorescence imaging and perform deep tissue detection with photoacoustic imaging. BPLPAT scaffolds demonstrated 3D high-spatial-resolution deep tissue photoacoustic imaging, as well as promoted the growth and differentiation of PC12 nerve cells. As such, the biodegradable dual-imaging-enabled electroactive BPLPAT will be a promising candidate for neuro-imaging and neurological disease therapy [36].

5 Biodegradable functional biomaterials for neuro-sensing

Neurological disorders generally accompany changes of certain neurotransmitters and biomarkers in the nerve system. Neurotransmitters are endogenous chemicals that are released from synaptic vesicles in synapses into the synaptic cleft to transmit signals from one neuron to another target neuron. Heretofore, more than 100 neurotransmitters have been identified, and they can be categorized according to their functions into excitatory and inhibitory neurotransmitters. The excitatory neurotransmitters (e.g., glutamate) stimulate a nerve cell to produce an action potential to transmit signals, while inhibitory

neurotransmitters (e.g., γ -amino butyric acid (GABA)) try to prevent the signal-transmission process. However, some neurotransmitters possess both excitatory and inhibitory properties (e.g., dopamine). Neurotransmitters play significant role in many brain functions such as behavior and cognition. They adjust muscle tone and heart rate, as well as regulate sleeping, appetite, consciousness, mood and memory [20]. Changes in the concentration of neurotransmitters have been associated with many mental and physical disorders. Acetylcholine was the first neurotransmitter discovered in the CNS and PNS. It is determined as the transmitter at the neuromuscular junction that connects motor nerves to muscles. It activates skeletal muscles in the somatic nervous system, and may either excite or inhibit internal organs in the autonomic system. Acetylcholine is also vital to enhance learning and memory ability, improve alertness, and sustain attention [171 -163]. Damage to the cholinergic system, which produces acetylcholine, in the brain has been demonstrated to be associated with Alzheimer's disease related memory deficits [174, 175]. Glutamate is the most common excitatory neurotransmitter, which is excitatory at well over 90% of the synapses in the human brain [21]. Dynamics of glutamatergic excitation is vital in normal physiological processes including synaptic plasticity, long-term potentiation, differentiation and apoptosis. However, abnormalities in glutamate transport are associated with many illnesses. Excessive glutamate release can overstimulate the brain and cause excitotoxicity, triggering neuronal degeneration and cell death. The excitotoxicity has been implicated in many neurological diseases including Parkinson's disease, Alzheimer's disease, Huntington disease, seizures, stroke, epilepsy, and amyotrophic lateral sclerosis [176, 177]. Dopamine is another vital neurotransmitter that regulates the reward and pleasure centers of the brain, controls the release of various hormones, and affects motor behaviors. The concentration of endogenous dopamine has been determined in the range of 0.01–1 μM in the brain of bovine, rats, and humans [178]. Various neurological disorders are related with the dysfunction of the dopamine system. For instance, Parkinson's disease has been associated with low levels of dopamine, and schizophrenia has been linked to high levels of dopamine [22, 23]. In addition to neurotransmitters, certain biomarkers are also measurable indicators of neurological states, demonstrating normal or pathogenic biological processes. Most nerve cells of interest are often not directly observable in typical clinical settings, so validated biomarkers are critically essential to help the diagnosis of neurological disorders, and track the response to therapeutic intervention [179]. There are many validated biomarkers that have been determined to support the diagnosis and therapy for neurological disorders. For instance, the deposition of β -amyloid peptides (A β) in plaques in brain tissue has been proposed to cause the neurodegeneration in Alzheimer's disease. Among the various A β species, $A\beta_{42}$ (a peptide with 42 amino acids) is the major constituent of the abnormal plaques in the brains of patients with Alzheimer's disease. It was found that most of the patients with Alzheimer's disease had decreased levels of $A\beta_{42}$ in their cerebrospinal fluids (CSF) [180, 181]. MHC class II, as another example, is a biomarker of microglial activation. Studies have shown that the expression of MHC class II to be higher in the putamen and substantia nigra, as well as in the hippocampus, temporal cortex, transentorhinal cortex, and cingulate cortex of the brains of patients with Parkinson's disease [179].

Based on the above discussions, quantitative detection of neurotransmitters and biomarkers in biological environments of urine, plasma, serum and CSF appears to be able to improve

the diagnosis and treatment process of neurological disorders. Surveys of literatures showed that functional biomaterials including electroactive biomaterials, magnetic biomaterials and photoactive biomaterials have been widely studied in the application of biosensing for neurotransmitters and biomarkers. For instance, Qian *et al.* developed conjugated polymer-based fluorescent nanoparticles with phenylboronic acid (PBA) on the surface for optical sensing of dopamine. The PBA works as binding sites for dopamine targeting. The nanoparticles, referred to as PFPBA-NPs, were utilized for fluorescence detection of neurotransmitter dopamine in both nerve cells PC12 and brain of zebrafish larvae. A good linear relationship was established between the fluorescence intensity ratio $(I_0 - I)/I_0$ of PFPBA nanoparticles and logarithmic concentration of dopamine in the range of 0.025–10 μM (where I_0 and I represent the maximum fluorescence intensity in the absence and presence of dopamine, respectively). The PFPBA-NPs also demonstrated a low detection limit of 38.8 nM, as well as a high specificity with minimum interference from other endogenous molecules such as glucose, ascorbic acid, tyramine, tyrosine, epinephrine, and norepinephrine. Therefore, the fabricated nanoparticles displayed high sensitivity and selectivity, allowing accurate detection of dopamine for diagnosis and therapy of dopamine related neurological diseases [182]. Kergoat et al. reported conducting poly(3,4-ethylene dioxythiophene):poly(styrene sulfonate)/platinum nanoparticle composites based organic electrochemical transistors (PEDOT:PSS/Pt NPs OECTs) for the detection of glutamate and acetylcholine. For glutamate detection, the PEDOT:PSS/Pt NPs OECT sensors presented a sensitivity of 4.3 A mol^{-1} L^1 cm^{-2} and a detection limit of 5 μM. For acetylcholine sensing, the OECT sensors demonstrated a sensitivity of 4.1 A mol^{-1} L^1 cm^{-2} and a detection limit of 5 μM. The detection limit of the OECT sensors was sufficient for the detection of glutamate in the extracellular fluid (typically in the low μM range), while not low enough for the sensing of acetylcholine in the extracellular fluid (typically in the nM range). The authors' ongoing work regarding the optimization of the nanoparticles dispersion in the PEDOT:PSS matrix is expected to improve the detection sensitivity and limit [183]. Li *et al.* applied magnetic nitrogen-doped graphene (MNG) to modify the Au electrode, and developed a reusable biosensor for the detection of amyloid-beta peptide 1–42 (Aβ42). To improve the detection specificity, antibodies of Aβ 1–28 (Aβab) that serve as the biorecognition element for Aβ42 were conjugated on the surface of MNG. The reusable biosensor showed presented a linear calibration curve within the range from 5 to 800 pg mL^{-1}, covering the cut-off level of Aβ42. It also achieved a detection limit of 5 pg mL^{-1}. The results demonstrated that fabricated biosensor possesses many advantages such as simplicity, high sensitivity and selectivity, quick response time, low cost, reproducibility, and stability, enabling a potential candidate for early diagnosis of Alzheimer's disease [18].

So far, very few biodegradable functional biomaterials have been involved in the application of biosensing of neurological disorders. Flexible and biodegradable electrochemical sensors reported by Pal *et al.* can be an example (Fig. 2) [40]. The sensors were fabricated using a benchtop photolithographic setup to format PEDOT:PSS micropattern on a flexible and fully biodegradable silk protein fibroin substrate. The resulting devices are mechanically flexible and optically transparent. Applying the conductive PEDOT:PSS micropatterns as working electrodes, the biosensors exhibited excellent electrochemical activity and stability over three days. The biosensors were applied for non-specific detection of dopamine and ascorbic

acid. For dopamine detection, the sensors showed a lowest detectable concentration of 15.21 μM and a quantitation limit of 46.1 μM. For ascorbic acid sensing, they demonstrated a lowest detectable concentration of 15.47 μM and a quantitation limit of 46.87 μM. The amperometric response curve of the dopamine exhibited a linear range from 10 to 200 μM, with a sensitivity of 45.9 nA μM^{-1} cm^{-2}. While the amperometric response curve of ascorbic acid had a linear range from 10 to 600 μM, with a sensitivity of 256.5 nA $\mu M^{"1}$ cm $^{-2}$. The response time (time taken to reach 95% of steady state current) for both dopamine and ascorbic acid was ~30 s. The linear and dynamic ranges for detection of dopamine and ascorbic acid of the fabricated sensors were comparable with other reported sensors. These sensors also presented high stability under mechanical stress. They were able to retain their physical integrity and electrochemical properties under repeated mechanical deformations of 150 bending cycles. Furthermore, the sensing devices were completely biodegradable under enzymatic action, and were able to be designed with programmable degradation rate through controlling the film crosslinking. Therefore, the reported technique is able to be used for the development of robust, biodegradable, sensitive, and inexpensive biosensors for dopamine and ascorbic acid detection. With further modification or incorporation with other electroactive species, biosensors with more specificity and sensitivity for the detection of neurotransmitters and biomarkers are expected to be developed to improve the diagnosis and treatment for neurological diseases.

6 Biodegradable functional biomaterial mediated therapy for neurological disorders

Functional biomaterials play essential roles in the treatment for neurological disorders by supporting and guiding the growth and differentiation of neuron cells in forms of scaffolds, by facilitating the delivery of drugs, neuroprotective agents, and growth factors across BBB in forms of nanocarriers [24, 184, 185]. Compared with traditional biomaterials, functional biomaterials based therapy could further provide physical stimuli using optical, electrical and magnetic methods to either regulate cell signaling directly or to control drug delivery with high precision and accuracy. Here, we focus on recent advances in the development of biodegradable functional biomaterials that may lead to strategies for nerve regeneration, neuroprotection, and brain tumor treatment. We highlight studies using conductive materials for electric stimulation of neuron activity and for electrochemical controlled drug delivery; magnetic materials for magnetic stimulation of neurons and hyperthernia treatment for brain tumor; photoactive materials for light stimulation of nerve activity and for optical fiber to deliver light; as well as examples of multifunctional biomaterials for theranostic applications. Lastly, the materials with intrinsic neuroprotective potential for neurological diseases will be discussed.

6.1 Biodegradable electroactive biomaterials for the treatment of neurological disorders

Electrically conductive materials have received marked attention in our effort towards promoting neuroregeneration, by means of either electric stimuli delivery or controlled release of therapeutic drugs, given the specific electric nature of neuron cells. In fact, electrical stimulation has long been applied in clinics with its therapeutic effect proven to improve a wide range of neurological disorders, including stroke, Parkinson's disease,

Alzheimer's disease [186], seizure [187], as well as to facilitate the functional rehabilitation after traumatic injuries either in CNS or in PNS [188]. Established modalities of electric stimulation therapy, non-invasive [186] (transcranial electric stimulation for CNS disorders and transcutaneous stimulation for PNS disorders) or invasive [189] (deep brain stimulation for CNS disorders and direct low frequency electric stimulation for PNS disorders), in combination with commercialized devices are available to promote neuron axon growth, to influence neurotrophic factors production, and to modulate neuron activity [190].

The noted beneficial effect of electrical stimulation makes the conductive materials an attractive candidate for functionalized scaffold, which allows the local delivery of electrical stimulus with temporal and spatial control, while supporting and guiding cell growth. Numerous evidence has shown that the locally delivered electrical stimulus is beneficial for nerve regeneration. For example, the direct current electric fields stimulation of 100 mV/cm delivered by the polypyrrole-block-polycaprolactone (PPy-PCL) biodegradable substrate for 2 h already increased the axon growth of the attached dorsal root ganglia by 21% (±3%) [191]. The axon outgrowth from neuron stem cell (NSCs) could also be guided in a controlled manner by combining a micropatterned PEG hydrogel with silver nanowire (AgNW), which led to a higher rate of axon directional outgrowth after electrical stimulation [182]. Moreover, rat PC12 cells cultured on both PPy doped poly (D,L-lactic acid) (PPy/PDLLA) [41] and aniline tetramer doped citrate based materials (BPLPAT) [36] have shown a marked increase in both the percentage of neurite-bearing cells and their median neurite length. Besides, Schwann cells that cultured on conductive poly (glycerol sebacate)-co-aniline pentamer (PGS-AP) exhibited enhanced myelin gene expression and neurotrophin secretion, which subsequently induced the neurite growth of PC12 cells (Fig. 3) [77]. The mechanism underlying the benefit of electrical stimulation through conductive materials is not fully understood. Different hypotheses have been proposed, and one compelling hypothesis is that electric stimulation might alter the protein adsorption behavior to conductive materials, thereby affecting cell-materials interaction [193]. Also, one recent study pointed out that conductive films affected the intracellular calcium level, which led to altered CaSR and PLCβ pathways for induced neurotrophin secretion [77]. Of note, up to now the application of those biodegradable conductive materials has mainly focused on the regeneration of peripheral nerves, and encouragingly, the conductive PPy/PDLLA guidance conduit has shown promising performance as evaluated by walking track, triceps weight, electrophysiological and histological assessment, similar to autologous graft in the functional repairing of rat sciatic nerve defects (Fig. 4) [41]. At the same time, conductive hydrogel-based materials are being explored as a coating for neural electrodes, which are used widely in the invasive electric stimulation therapy, to regulate the electrode modulus and to improve its biocompatibility. Although currently non-degradable hydrogels are focused for this coating purpose, efforts have been made towards the development of degradable coating hydrogels. For instance, a biodegradable conductive hydrogel composed of degradable agarose and aniline petramer (AP) [194] was developed. The resultant hydrogels presented enhanced ions and electrons mobility, as well as improved cytocompatiblilty, serving as a potential candidate for different applications in neuron tissue engineering.

In addition to modulating cell activity, conductive materials have also shown their potential to electrochemically control the release of drugs based on the ability to electrically switch the oxidized and reduced state of the polymer, leading to uptake and expulsion of charged drugs from the bulk materials [195]. Many therapeutic and neuroprotective drugs, including neurotransmitter dopamine, antiinflammatory factor dexamethasone, as well as neuroregenerative neurotrophin-3 and brain-derived neurotrophic factor (BDNF), have already been bound and released from PPy-based conductive polymers [196]. There is also ongoing effort to develop biodegradable conductive materials that are capable of electrochemically controlled drug release. For example, biodegradable multiblock copolymer composed of oligoaniline and PEG or poly(ε-caprolactone) (PCL) has been shown to possess a drug loading as high as 31 wt%, and deliver dexamethasone phosphate triggered by potential cycling between 0.7 V and −0.5 V [196]. Also, the release profile can be tailored by simple modulation of the electrical input and the stimulation cycle numbers. Similarly, a voltage-dependent releasing of dexamethasone was achieved by using the conductive agarose-AP hydrogel [194]. Together with the proven cytocompatibility, this new series of conductive polyesters and hydrogels possess the potential to develop an advanced system for future management of neurological disorders by integrating electrochemically controlled drug delivery system with electrical stimulation enabled tissue scaffolds.

6.2 Biodegradable magnetic biomaterials for the treatment of neurological disorders

Direct techniques to alter neural activity also include magnetic stimulation by applying magnetic fields near the scalp to induce electric fields within the brain to modulate neuron activities [188], in addition to electrical stimulation. Disorders such as Parkinson's disease, epilepsy and stroke rehabilitation were treated with the magnetic stimulation and have shown therapeutic efficacy [186]. In fact, magnetic techniques offer distinct benefits for *in vivo* applications, given magnetic fields can penetrate deeply into biological tissue without significant attenuation [197]. Importantly, in combination with magnetic nanoparticles, magnetic field could also be transformed into heat [198, 199], as well as into mechanical force [200].

Increasing evidence has shown that magnetic iron oxide nanoparticles can also serve as potent photothermal agents to modulate neuron cell activity, evidenced by an exciting study using superparamagnetic ferrite nanoparticles to bind to specific cells expressing the temperature sensitive ion channel TRPV1 [198, 199]. After applying a radiofrequency magnetic field, the nanoparticles heating led to the opening of TRPV1 channels and calcium influx was observed. A similar strategy using polymer encapsulated magnetic manganese ferrite nanoparticles, when binding to the neurons in the motor cortex which were transfected to express TRVP1 channels [199], has confirmed the capability of opening TRVP1 channel via heating the nanoparticles, which further resulted in deep brain stimulation in the striatum caused rotation. This study provided proof of principle for the magnetic-based deep brain control of movement for the treatment of motor nerve derived neurological diseases, such as amyotrophic lateral sclerosis (ALS). Of interest, the electromagnetic fields (EMF) at specific range generated by electrically charged subject, can also influence cell function and even guide cell differentiation. Specifically, a specific frequency and intensity of EMF stimulation (2×10^{-3} T/100 Hz) has been found to

dramatically improve the efficacy of direct lineage reprogramming of somatic fibroblasts [201], in the presence of reprogramming transcription factor, into induced dopaminergic neurons both *in vitro* and *in vivo,* which represents a viable and promising therapeutic strategy to replace lost neurons in neurodegenerative diseases such as Parkinson's disease with high efficiency, low toxicity and high controllability. Moreover, the underlying mechanism for the EMF mediated cell reprogramming was due to the promoted chromatin remodeling which enabled the transcriptional changes necessary for the reprogramming process.

Magnetic field induced heat has also been applied in the hyperthermia therapy, named magnetic hyperthermia, for the treatment of glioblastoma, based on the fact that tumor cells are more sensitive to sudden increases in temperature than the normal surrounding cells, leading to selectively tumor cell death [200]. The magnetic hyperthermia offers advantages in generating a homogenous distribution of therapeutic temperature in deep and inaccessible tissues. Evidence has shown that SPIONs are appropriate intratumoral hyperthermia agents. Their design requirements, *in vitro* application, as well as preclinical and clinical application have been reviewed elsewhere [200]. In addition to the magnetothermal effect, magnetic field on nanoparticles can also be transformed into mechanical force. Together with the surface modification with targeted ligand, the nanoparticles could generate a force usually in the femtonewton range on the membrane receptors or could lead to receptor clustering, thereby influencing cell function. For example, by conjugating with monoclonal antibody for DR4 receptors, zinc-doped iron oxide magnetic nanoparticles selectively bound to the DR4 receptor on cancer cells, which induced clustering of the DR4s by using a magnetic field in a non-invasive manner [202], leading to the activation of apoptotic signaling pathways. Although still at the early stage of development, this new technology offers the potential of applying magnetic techniques in spatially and temporally activation of cell death or other signaling pathways at the target region for the treatment of neurological diseases, such as glioblastoma.

With all above emerging studies showing the controllability and feasibility for the therapy design and precise imaging of neurological disorder that is brought by magnetic materials, it would be promising to further functionalize the magnetic nanoparticles with other types of functional biomaterials, to not only improve cytocompatibility and introduce additional functionality, but also allow easy loading and controlled releasing of therapeutic drugs [203-205]. Coating of magnetic nanoparticles with temperature sensitive polymers [203], could serve as a good example, as the increased temperature generated through magnetic nanoparticles was found to increase the releasing of doxorubicin controllably in a temperature-dependent manner. A coating of polymers on magnetic nanoparticles could also provide an easier way for further surface modification to prepare "smart" nanoparticles. For example, after encapsulating magnetic nanoparticles using (dodecyl-grafted-poly-(isobutylene-alt-maleic-anhydride) (PMA) polymer [199], the polymer coating was further modified with NeutrAvidin, which mediated the binding of the resultant nanoparticles to biotinylated neuronal cell membrane. Dylight 550 fluorophores was also conjugated to the polymer as molecular thermometers, to monitor the cell surface temperature changes. Similarly, by coating magnetic nanoparticles with cationic polyamine dendrimer, it allowed better siRNA loading while aiding the escape of siRNA from endosomes [206]. More

importantly, a marked increase in transfection efficiency to promote neural stem cell differentiation was achieved by applying external magnetic field, named magnetic facilitated drug delivery. Given the critical role of NSCs in nerve regeneration and treatment of neurological diseases, the above studies strongly suggest the promising application and the essential role of those composite magnetic materials, especially those in combination with biodegradable functional biomaterials, for the future treatment of neurological disorders. By composting magnetic nanoparticles with a biodegradable chitosan-glycerophosphate polymer, Liu et al. developed a new magnetic nanocomposite scaffold with tunable magnetization and degradation rate (Fig. 5). The resultant scaffold could be synergized with applied magnetic field, not only to enhance the viability of Schwann cells *in vitro,* but also to promote the nerve regeneration and functional recovery of a 15 mm sciatic nerve defect in rats [42], representing as a promising therapy for peripheral nerve regeneration.

6.3 Biodegradable photoactive biomaterials for the treatment of neurological disorders

The interest of using photoactive materials for the treatment of neurological diseases arises from the potential of modulating cell behavior and activity through direct low-intensity pulsed light stimulation [186] and via the material mediated photothermal therapy [104, 207]. In fact, despite less common and mostly performed in experimental settings, there is transcranial light therapy and peripheral nerve light stimulation studies available, which have shown its effect to enhance regional cerebral blood flow, increase neuron activity, and modulate mitochondrial function [186]. Also, studies have shown that the excitation of nerve cells by direct light illumination is largely because of the transient photothermal effect, represented by the generated thermal gradients surrounding the nerve tissue (6°C-10°C), resulting in direct or indirect activation of transmembrane thermo-sensitive ion channels to regenerate action potential [99]. Given the penetration depth of therapeutic light is limited, Kuo *et al.* also performed deep brain light stimulation in a rat using a fiber-coupled laser stimulator at wavelength of 840 nm with the pulse repetition rate of 130 Hz [208]. Experimental results showed the favorable effect of light stimulation on decreasing the glutamate concentration while increasing the dopamine production in the striatum, which demonstrated its potential application in the treatment of dopamine related diseases such as Parkinson's disease. In addition, hybrid optoelectronic systems consisting of an electronic circuit, an optical fiber, and a photoelectrical converter, have been developed for electrical stimulation of hippocampal living neurons [209]. In the new system, an optical fiber instead of conventional metallic wires was utilized, placing between the electronic circuit and stimulated neurons to provide galvanic isolation from external electric fields and prevent electromagnetic noise. The resultant optoelectronic system was shown to be effective for stimulating the electrophysiological activities of living neurons in the hippocampus, possessing potential to restore regions of brain activity after brain damage in traumatic brain injury or neurodegenerative diseases. Of note, the progress that made in the development of biodegradable optical fibers, such as the PLLA [210] or citrate-based material derived optical fiber [136], open up new avenue to explore the next generation of deep tissue light delivery systems to modulate neuron activity. In fact, in one most recent study, Fu *et al.* has proceeded to demonstrate the feasibility of using PLLA degradable optical fiber in applications such as intracranial light delivery, deep brain fluorescence sensing and optogenetic interrogation in mice [38], representing as a big step ahead towards the

development of fully biocompatible and biodegradable photonic systems for neuroscience uses.

Compared with electrical stimulation and chemical stimulation through therapeutic drugs, direct light stimulation offers improved spatio-temporal resolution. Moreover, the emergence of optogenetics, which combines light stimulation with genetic modification of target cells with light-responsive ion channels, enabled researchers to selectively excite or inhibit a subpopulation of neurons in neural tissues [101], but the imperative targeted gene modification of cell before light stimulation makes the clinical translation more challenging [101, 207]. To address this problem, non-genetic optical stimulation technique taking advantage of photothermal agents as transducers that absorb light and convert it into heat, has been designed to modulate neuron activity with higher specificity. For example, Yoo *et al.* developed a near-infrared activatable system which could inhibit the neuron activity by binding the gold photothermal nanorods onto cell membrane [207]. More importantly, such an inhibitory effect can be reversed by removing the light source and the degree of inhibition could be tuned by changing the laser intensity, indicating its potential application in the anti-epilepsy therapy by selectively suppressing the hyperactive neurons. In addition, light sensitive conjugated polymers, such as poly(3-hexylthiophene) (P3HT) in a form of thin films could also serve as a platform to optically modulate the membrane depolarization and hyperpolarization mediated by a thermal effect, with potential applications in neurological disease treatment [28]. Although the existing photothermal agents including metal nanoparticles, carbon nanomaterials, and organic photothermal agent, are not degradable, they have been successfully incorporated into matrices of soft materials, including polymer and gels which can be remotely controlled by light irradiation [211], representing tremendous opportunities for future exploration of a wide range of light activatable systems towards the treatment of neurological diseases.

6.4 Biodegradable multi-functional biomaterials for the treatment of neurological disorders

As mentioned above, the functional biomaterials enable multimodality of imaging, allows physical stimulated cell function and drug releasing, and permits further surface modification of targeted ligand for therapeutic purposes. Further, by combining different functional biomaterials, multifunctional systems, which is greatly desired for the optimal management of various neurological diseases, can also be developed to address the multi-dimension of CNS disorders. To this end, the most common way is compositing of different functional biomaterials. For example, encapsulation of magnetic nanoparticles with intrinsic fluorescent citrate-based materials [120] enables drug delivery with magnetic and fluorescent dual-imaging capability. A gold coating on magnetic nanoparticles can provide a number of additional advantages, such as near-infrared absorption for heat conversion and a facile surface for further functionalization to generate core-shell multimodal nanoparticles [206]. Similarly, other core-shell nanoparticles using biodegradable polymeric materials as the core structure to deliver therapeutic drugs while generating gold nanoshells combined with magnetic nanoparticles, have been developed as a multi-functional platform for simultaneous diagnosis through MRI, in combination with dual therapeutic modality of chemotherapy and NIR photothermal therapy [204]. In addition, the development of

multifunctional biomaterials, which could possess multiple interesting properties, such as the citrate-based biodegradable materials, offers unique opportunity to establish such a multitask platform. The conductive BPLPAT mentioned above, could serve as a good example, as it enables dual fluorescent and photoacoustic imaging while presented with conductivity allowing electrical stimulation by itself, after incorporating AT oligmer into citrate-based material framework (Fig. 6) [36]. Notably, citrate-based materials possessing numerous pendant carboxyl groups provide further designability to modify the materials with biology moieties [212], such as the targeted ligands to direct selective binding to the disease lesion, and the bioactive parts that exerting neuroprotective and neuropromotive potential. In fact, elastic yet strong citrate-based materials CUPE has been made into nerve conduit, which was further modified using folic acid, the small molecule was recently found to promote the neurotrophin production and stimulate neuronal differentiation [213].

Interestingly, increasing evidence points out that some elements releasing from materials could affect neuron activities, which potentially adds intrinsic biological regulatory capability into functional biomaterials, making them very promising for the treatment of neurological diseases. For example, magnesium has been found to induce neural depolarization [214]. In particular, citrate, one key building block for citrate-based materials, is considered to exert regulatory function in CNS probably by chelation with Ca^{2+} and Mg^{2+}, playing a pivotal role as a regulator for glutamate receptors [215], Although the exact physiological role of citrate in CNS remains unclear, a beneficial effect of citric acid on reducing brain oxidative stress and preventing neuronal injury of rats with acute exposure of malathion, a neurotoxic agent [216], has been reported. Similarly, citric acid was shown to attenuate the endotoxin-induced oxidative stress of the brain in another animal study, presented by inhibited lipid peroxidation and decreased inflammatory factor TNF-α production, strongly suggesting the innate neuroprotection nature of citrate molecule [217]. More importantly, by incorporating native anti-oxidant agent ascorbic acid into polymer network [218], a citrate-based materials poly (1,8-octanediol-co-citrate-co-ascorbate) (POCA) with intrinsic anit-oxidant and potential neuroprotective properties, in terms of scavenging of free radicals, iron chelation and the inhibition of lipid peroxidation, has been reported, making it a promising basal biodegradable materials for the treatment of neurological diseases, since oxidative stress and inflammation have been implicated in almost all neurological disorders and their associated secondary injuries [44].

7 Conclusion

This manuscript summarized the recent progress of biodegradable functional biomaterials, specifically biodegradable electroactive biomaterials, biodegradable magnetic biomaterials, and biodegradable photoactive biomaterials for diagnosis and treatment of neurological disorders. Compared to other biodegradable biomaterials, biodegradable functional biomaterials have the unique property of being responsive to external stimulation fields, enabling them with great powers to modulate cellular activities for nerve regeneration, to sense neurotransmitters and biomarkers for disease diagnosis, to perform non-invasive bioimaging for neural stem cell and disease tracking, to facilitate drugs and small molecules to cross BBB for disease targeting, as well as to achieve controlled drug release and hyperthermia treatment for neurological disease therapy. Despite the fact that biodegradable

functional biomaterials have shown impressive benefits in understanding and treating neurological disorders in preclinical research, their broad clinical adaptation and application will depend on further exploration and optimization. For instance, for better understanding and optimization of biodegradable functional biomaterials for the management of neurological disorders, we have to uncover how these biomaterials behave *in vivo,* and this is where more advanced bioimaging and biosensing techniques are of great importance. In addition, advanced nanofabrication techniques and surface modification approaches may endow biodegradable functional biomaterials with more sophisticated nanostructures to improve biocompatibility and cell/material interactions. Furthermore, the combination of biomaterials and stem cell therapies is emerging to revolutionize neurological disorders treatment [62], we believe the introduction of biodegradable functional biomaterials to stem cell therapies would significantly improve the therapy results through providing better controlling of neural stem labeling, transplantation, and differentiation. It is our belief that at this materials-design age, the innovation of functional degradable biomaterials will spur the search of solutions to tackle the challenges in neurological disorder management.

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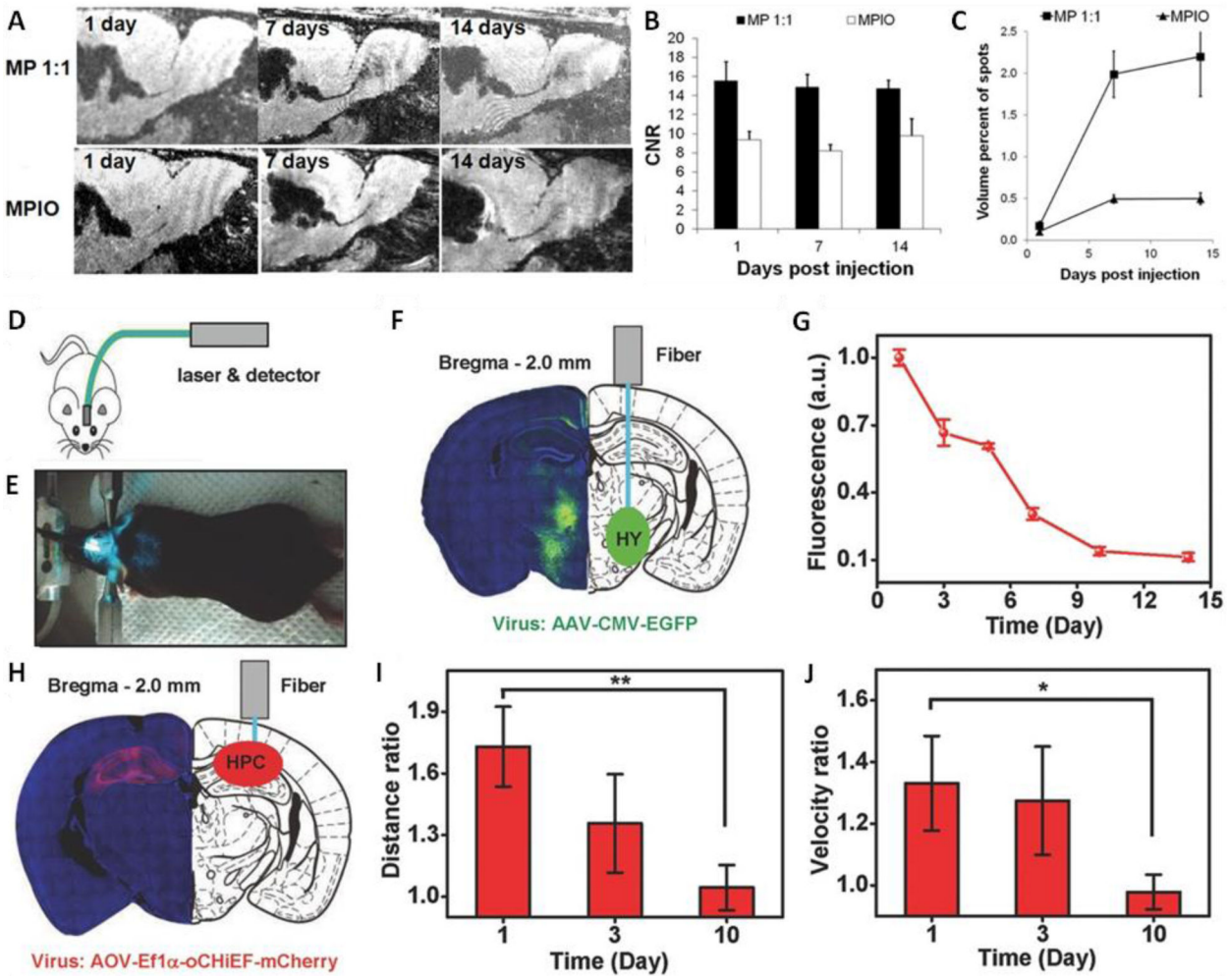

Fig. 1.

Biodegradable functional materials for neuro-imaging. (A-C) *In vivo* MRI of the migration of endogenous neural progenitor cells in rat brain. (A) MRI montage of same animal at level of SVZ –RMS –OB injected with microparticles (MP) or inert MPIOs. (B) CNR measurement of dark contrast within RMS. (C) Volume of dark contrast in the OB. (D-J) *In vivo* fluorescence photometry and optogenetic experiments with PLLA optical fibers. (D) Schematic cartoon of the experiment design and setup. E) Photographic image of the experiment setup. F) Left: confocal microscopic image of a coronal section containing EGFP. Right: schematic illustration of the fiber implanted into the HY. G) Fluorescence signals recorded via PLLA optical fibers (standard deviation, $n = 6$) normalized to those measured via silica fibers. H) Left: confocal microscopic image of a coronal section containing oCHiEF protein. Right: schematic illustration of the fiber implanted into the HPC. I) Ratio of travelling distance with the laser on and off. J) Ratio of travelling velocity with the laser on and off. Abbreviations: SVZ, subventricular zone; RMS, rostral migratory stream; OB, olfactory bulb; MP, microparticle; MPIO, micron sized iron oxide particle; CNR, contrast to noise ratio; EGFP, enhanced green fluorescence protein; HY, hypothalamus; HPC, hippocampus. Reproduced from Ref. [38] with permission of John Wiley and Sons.

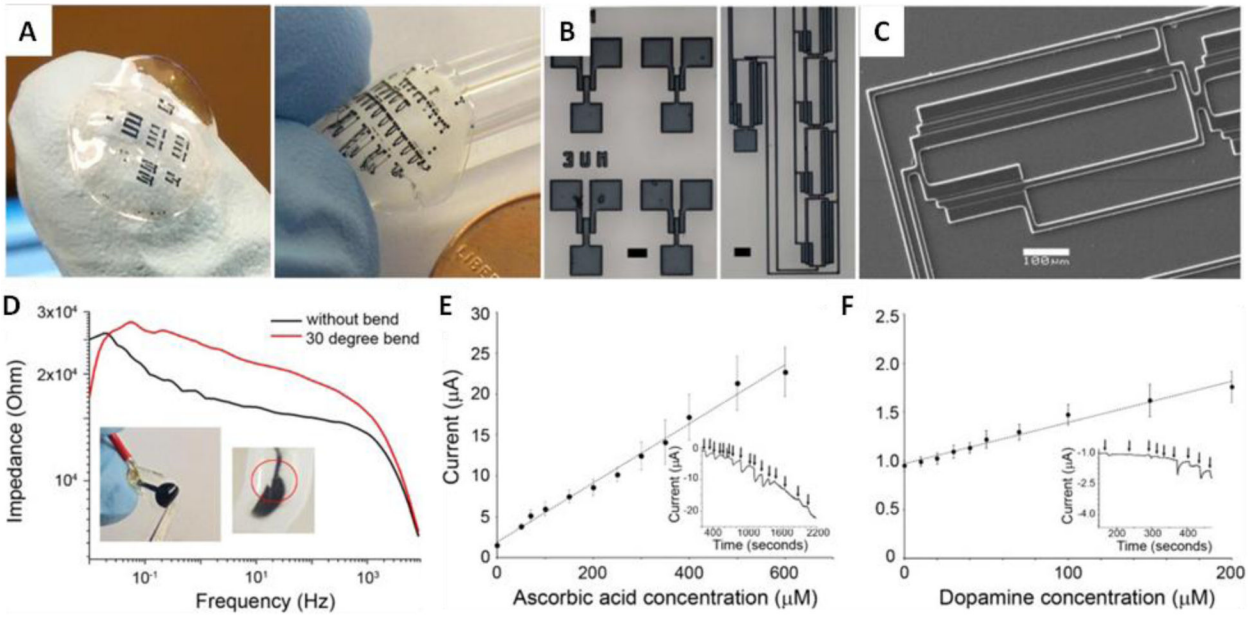

Fig. 2.

Biodegradable functional materials for neuro-sensing. (A) Large area micropatterns of PEDOT:PSS formed on flexible and conformable silk fibroin sheets via photolithography. (B) Optical micrographs and (C) SEM images of PEDOT:PSS micropatterns on glass. (D) Mechanical bending and corresponding effect on impedance after 150 bending cycles. Non-specific sensing of (E) ascorbic acid and (F) dopamine biosensing, showing the linear ranges of both sensors (R2=0.989 and 0.979 respectively with n=3 sensors). The insets show the chronoamperometric response with addition for one sensor as an example. Reproduced from Ref. [40] with permission of Elsevier.

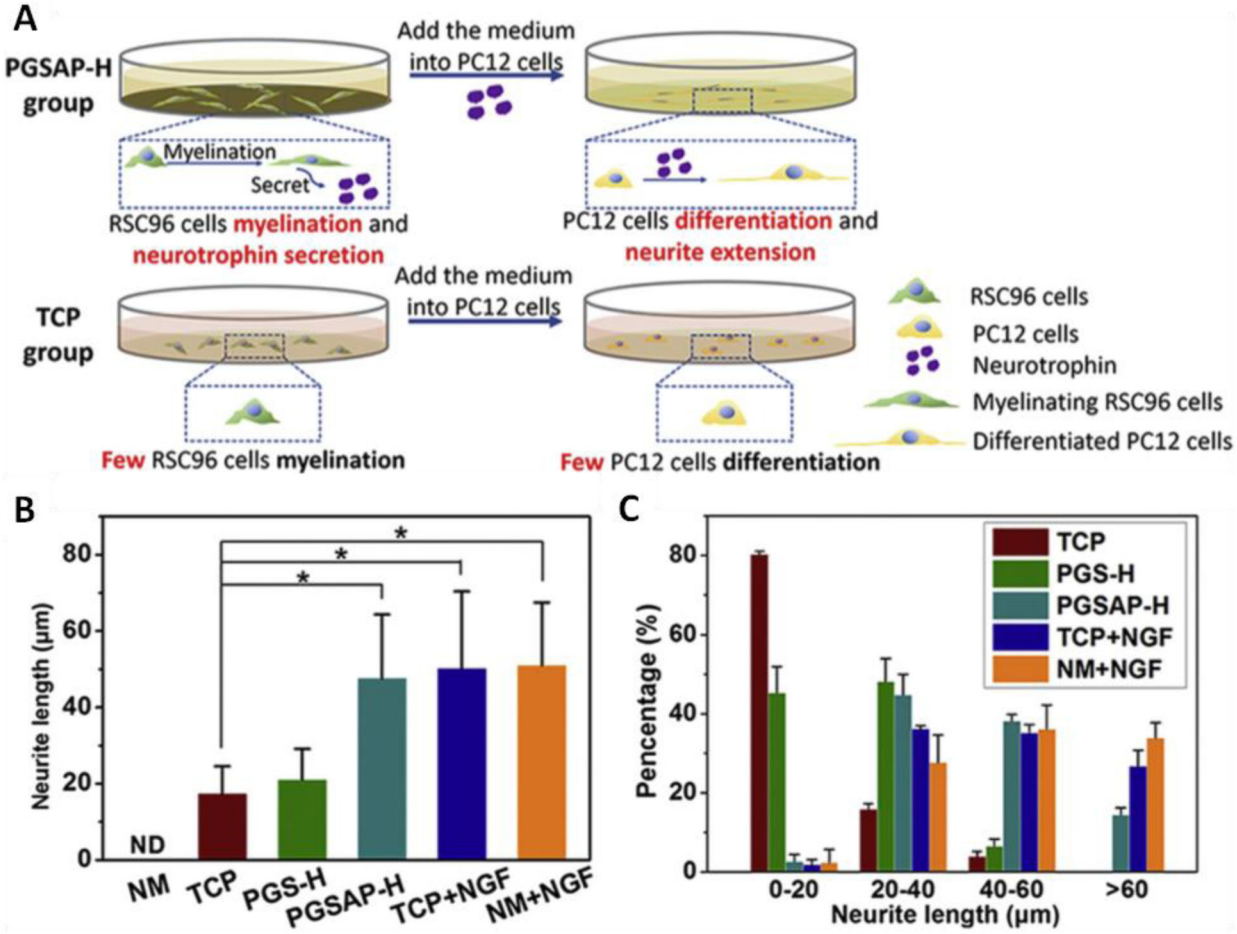

Fig. 3.

Schwann cells-laden conductive PGSAP-H films inducing PC12 cells differentiation. (A) Schematic diagram depicting PC12 cells differentiation and neurite extension when culture in medium suspension from Schwann cells (RSC96) on conductive films. (B) Quantitative analysis of neurite length of PC12 cells supplemented with the normal medium (NM) group, TCP group, PGS-H group, PGSAP-H group, TCP + NGF group, and NM + NGF group. (d) Frequency of neurite length distribution of PC12 cells of each group. *P < 0.05. Reproduced from Ref. [77] with permission of Elsevier.

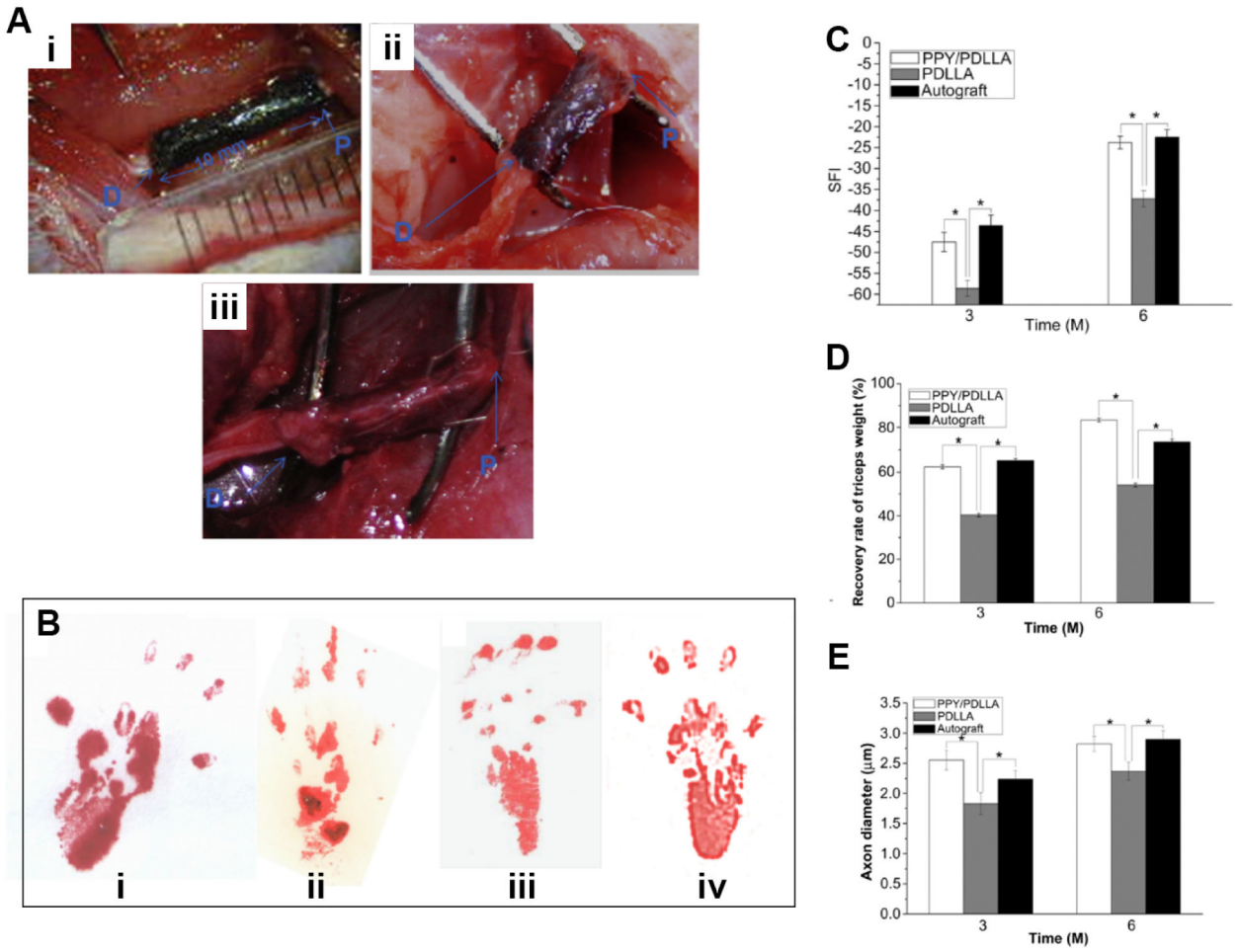

Fig. 4.

Conductive PPy/PLLA conduit for the regeneration of 10-mm sciatic nerve defects. (A) Intraoperative photographs of the PPY/PDLLA nerve conduit implantation. “P” indicates the proximal end and “D” indicates the distal end. i) Immediately after grafting. ii) 3 months postoperatively. iii) 6 months postoperatively. (B) Footprint stamps in walking track analysis after 6 months of implantation. Groups: i) PPY/PDLLA. ii) PDLLA. iii) Autograft. iv) Normal left leg. (C) Sciatic function index (SFI) as a function of implantation time. (D) Triceps weight (%) evaluation after 3 and 6 months post-operation (n= 6, * indicates $p < 0.05$). (E) Average axon diameter of regenerated myelinated nerve fibers. Reproduced from Ref. [41] with permission of Elsevier.

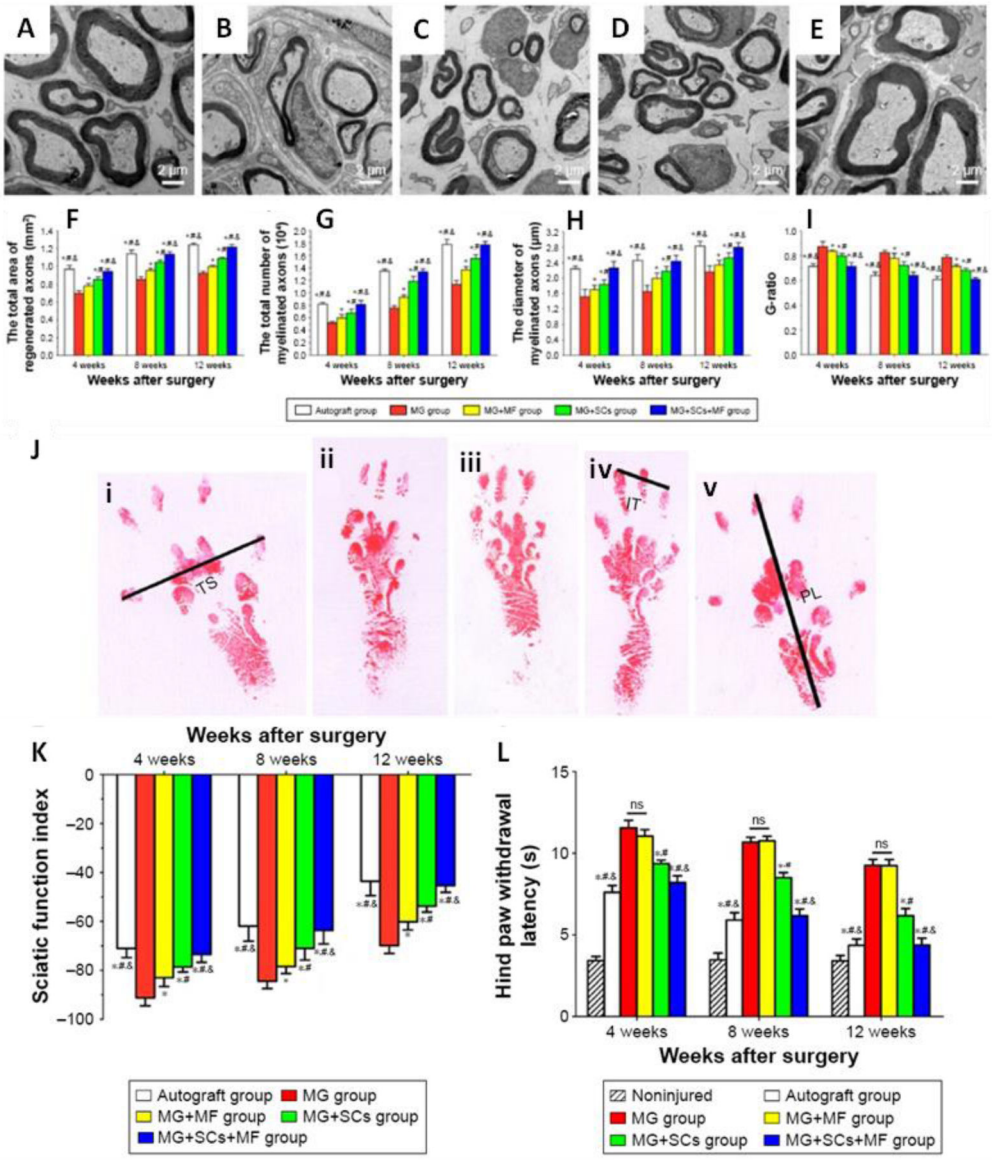

Fig. 5.

Morphologic appearance and morphometric assessments of regenerated nerves in each group. (A-E) The characteristic electron micrographs of regenerated axons in the middle part of the scaffold in the (A) autograft group, (B) MG group, (C) MG+MF group, (D) MG+SCs group, and (E) MG+SCs+MF group at 12 weeks postoperation. (J-K) The sciatic functional index in each group. (F) The cross-sectional area of regenerated nerves in the scaffold. (G) Quantitative analysis of myelinated axons in the scaffold. (H) The diameter of myelinated axons in the scaffold. (I) The G-ratios in the scaffold. (J) The operative left footprints at 12 weeks postoperatively. i) Autograft group. ii) MG group, iii) MG+MF group. iv) MG+SCs group. v) MG+SCs+MF group. (K) The statistical data of the sciatic functional index. (L) The hind paw withdrawal latency time. *p<0.05 compared to MG group; #p<0.05 compared to MG+MF group; &p<0.05 compared to MG+SCs group; all results are presented as the mean ± standard eror of the mean. Abbreviations: MG, the rats were bridged with the

magnetic scaffold; MG+MF, the rats were bridged with the magnetic scaffold and under MF exposure after surgery; MG+SCs, the rats were bridged with the Schwann cells-loaded magnetic scaffold; MG+SCs+MF, the rats were bridged with the Schwann cells-loaded magnetic scaffold and under MF after surgery; MF, magnetic field; SCs, Schwann cells. IT, intermediary toe spread; PL, print length; TS, toe spread. Reproduced from Ref. [42] with permission of Dove Medical Press.

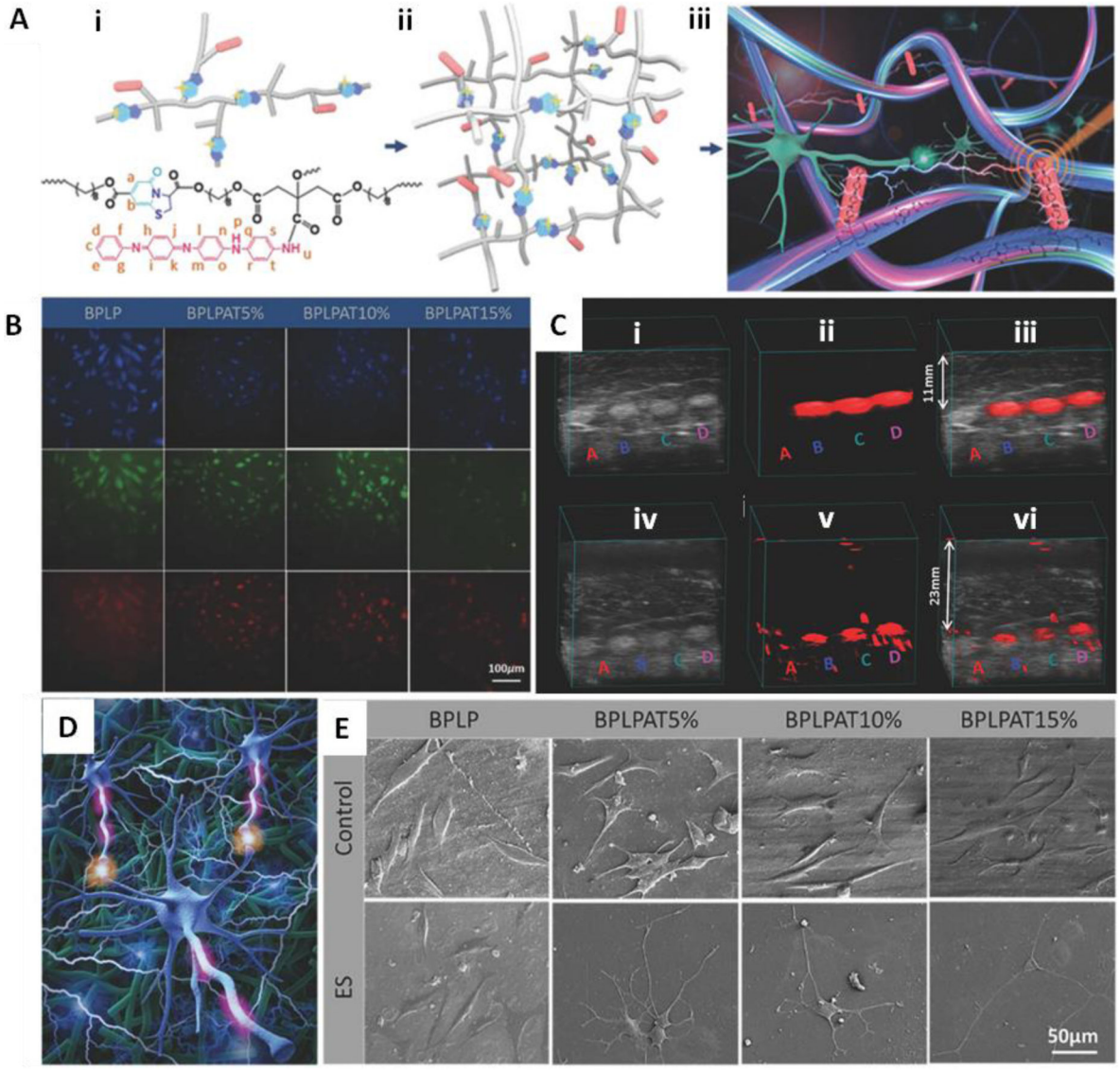

Fig. 6.

Citrate-based fluorescence/photoacoustic dual-imaging enabled biodegradable electroactive polymers. (A) i) Schematic and chemical structure of BPLPAT pre-polymers. ii) Schematic of cross-linked BPLPAT structure. iii) Schematic of functionalities of crosslinked BPLPATs. (B) Fluorescence imaging of PC12 cells uptaken with BPLP and BPLPAT nanoparticles. (C) i) Ultrasound images, ii) photoacoustic images, and iii) superimposed ultrasound and photoacoustic images of BPLP and BPLPAT scaffolds under a ~11 mm thick layer of chicken breast tissue. iv) Ultrasound images, v) photoacoustic images, and vi) superimposed ultrasound and photoacoustic images of BPLP and BPLPAT scaffolds under two layers (total ~23 mm thick) of chicken breast tissue. (D) Schematic of electrical stimulation of PC-12 cells on cross-linked BPLPAT materials. E) SEM images of PC-12 cells on BPLP and BPLPAT films without electrical stimulation (control) and with electrical stimulation. Reproduced from Ref. [36] with permission of John Wiley and Sons.