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Advanced theragnostics for the central nervous system (CNS) and neurological disorders using functional inorganic nanomaterials

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ABSTRACT

Various types of inorganic nanomaterials are capable of diagnostic biomarker detection and the therapeutic delivery of a disease or inflammatory modulating agent. Those multi-functional nanomaterials have been utilized to treat neurodegenerative diseases and central nervous system (CNS) injuries in an effective and personalized manner. Even though many nanomaterials can deliver a payload and detect a biomarker of interest, only a few studies have yet to fully utilize this combined strategy to its full potential. Combining a nanomaterial's ability to facilitate targeted delivery, promote cellular proliferation and differentiation, and carry a large amount of material with various sensing approaches makes it possible to diagnose a patient selectively and sensitively while offering preventative measures or early disease-modifying strategies. By tuning the properties of an inorganic nanomaterial, the dimensionality, hydrophilicity, size, charge, shape, surface chemistry, and many other chemical and physical parameters, different types of cells in the central nervous system can be monitored, modulated, or further studies to elucidate underlying disease mechanisms. Scientists and clinicians have better understood the underlying processes of pathologies for many neurologically related diseases and injuries by implementing multi-dimensional 0D, 1D, and 2D theragnostic nanomaterials. The incorporation of nanomaterials has allowed scientists to better understand how to detect and treat these conditions at an early stage. To this end, having the multi-modal ability to both sense and treat ailments of the central nervous system can lead to favorable outcomes for patients suffering from such injuries and diseases.

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1. Introduction

The central nervous system is a vital component of human physiology that coordinates movement and responses, affects behavior and cognitive function, and regulates physiological function by receiving and processing sensory information while outputting motor signals. Recent advances in biomedical engineering have allowed researchers to design nanomaterials (NMs) that can interface with the CNS to modulate cell fate and behavior while monitoring key biomarkers. Furthermore, numerous biological and biomedical processes take place on the nanoscale (e.g., cellular uptake, signal transduction, neurotransmitter release, and drug delivery). Thus, having the ability to monitor and modulate these activities via theragnostic nanomaterials allows for precise diagnosis and the ability to influence a myriad of biological processes.

Inorganic nanomaterials have been heavily utilized to monitor and modulate CNS processes due to their unique and tunable properties. These innate properties arise from the chemical composition and crystal structure that compose the nanomaterial. For example, iron oxide nanoparticles can respond to an external magnetic field as an intrinsic property of the material. By modulating the crystal structure and doping various divalent metal ions into the host, such as zinc and manganese, it is possible to increase the magnetic susceptibility and improve the magnetic resonance imaging (MRI) imaging capabilities of these materials. Similarly, gold nanomaterials can have their size, charge, and dimensionality easily tuned to provide specific emission profiles, control their surface plasmon resonance, and determine which cells they have an affinity towards entering. Moreover, upconversion nanoparticles can have their emissions tuned by doping the appropriate percent of lanthanides into the host matrix, activating light-controllable receptors, and spatiotemporal release of drugs using near-infrared (NIR) light. Thus, the inorganic material can be utilized actively to diagnose and/or treat conditions of the CNS, as will become evident in later sections.

We define theragnostic nanomaterials as those that facilitate the delivery of a therapeutic agent while also lending themselves to biomarker detection and/or enhanced imaging capabilities. Summarizing the knowledge gained from these discoveries will assist scientists in developing advanced nanomaterials to improve the treatment of neurological disorders and injuries, as well as earlier diagnosis of these conditions. Currently, limitations of applying nanomaterials to theragnostic applications in the CNS include, but are not limited to, crossing innate biological barriers without causing damage (i.e., the blood-brain-barrier [BBB] and the blood-cerebrospinal fluid barrier) [1], an incomplete understanding of underlying biological processes [2,3], and the inability to identify biological markers and administer disease-modifying treatments at an early disease-state (i.e., when the patient is asymptomatic) [4]. With these limitations in mind, we will discuss various approaches utilized within the field of CNS research for the treatment, monitoring, and combined theragnostic use for injuries and diseases in the CNS. Moreover, we will discuss inorganic nanomaterials that can be utilized in probing underlying mechanisms and differentiating/transdifferentiating cells into neuronal or glial cell lineages for future treatment options. Specifically, we will dive into multi-dimensional nanomaterials, such as zero-dimensional (0D), one-dimensional (1D), and two-dimensional (2D) nanomaterials, and how they have been utilized in the aforementioned situations [FIGURE 1]. In addition to their ability to interface on the nanoscale, these inorganic nanomaterials are often less invasive than traditional transplant materials, may be directed towards specific cells, and may degrade or be cleared from the CNS and body over time, giving them considerable advantages over traditional medical procedures and untargeted therapeutics. To this end, it is of great importance that novel nanomaterials are designed to elucidate underlying mechanisms or lessen disease progression while simultaneously detecting biomarkers and imparting imaging capabilities.

2. Challenges In The Theragnostics Of Neural Disorders

2.1. Diagnostics of Neural Conditions and Injuries

Central nervous system disorders, manifesting as the loss of normal neuronal functions, may be induced by various reasons, such as brain tumors, spinal cord injury, and neurodegenerative diseases. The extreme complexity of the CNS makes precise diagnosis challenging. Many neurological disorders happen without distinguished symptoms, definitive causes, and unique markers, making evaluation and diagnosis of neural conditions more elusive. Early detection of CNS disorders will allow therapeutic interventions at the preclinical stage and offer a chance to carry out appropriate neuroprotective measures to slow disease progression. Current clinical diagnostics for neurological conditions integrate cognitive behavioral assessment with brain neuroimaging technology, such as CT, MRI, and PET [5]. However, many neurodegenerative diseases, such as AD, PD, and Huntington's disease (HD), will experience a long prodromal period (i.e., before the earliest symptoms occur) [6]. The assessment of cognitive and behavioral ability is not conclusive enough to diagnose certain neurological disorders. With the advancement of imaging technology, brain imaging for visualizing solid tumors or specific marker accumulation can be

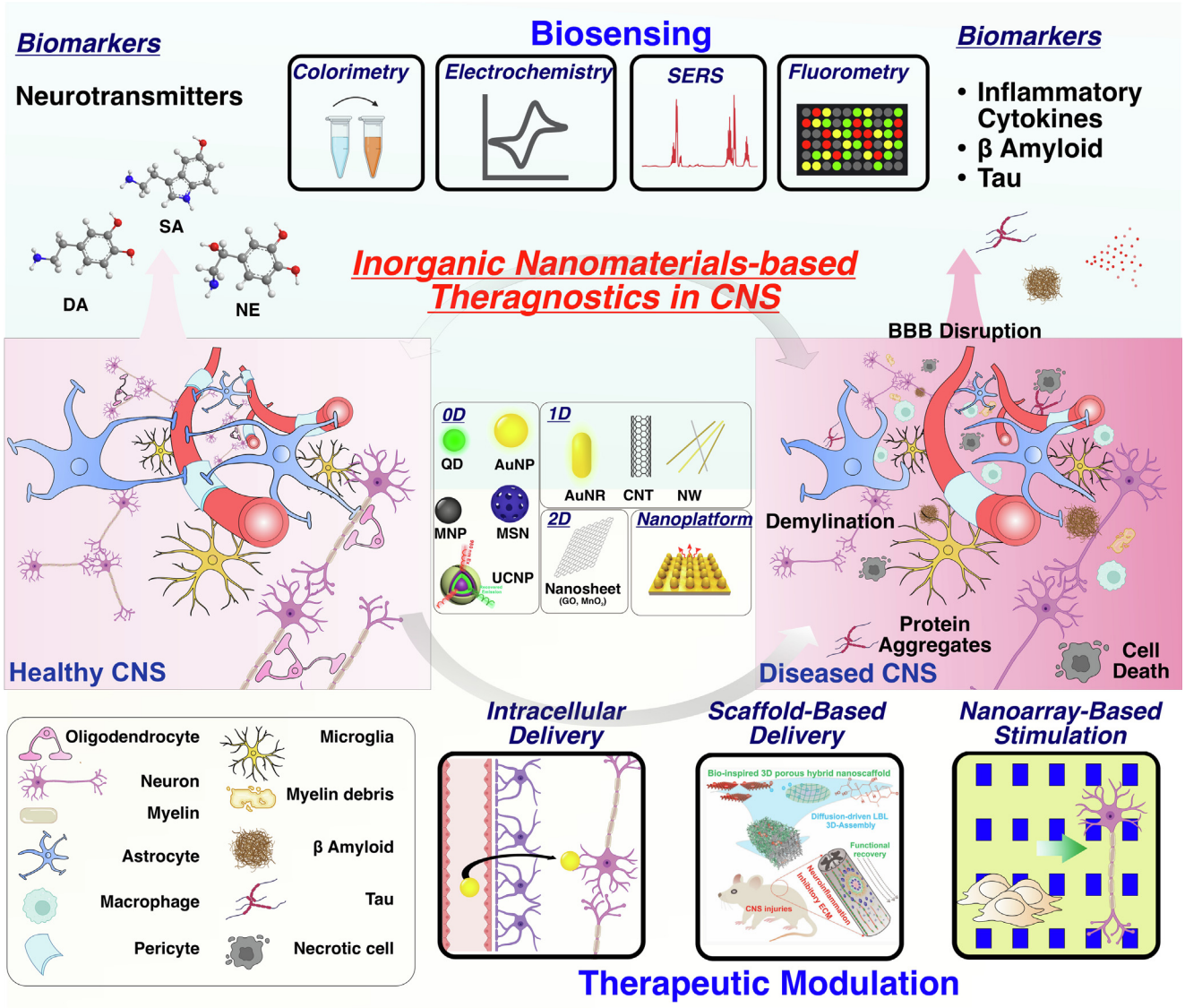

Figure 1. Applications of inorganic nanomaterials for theragnostics in the central nervous system. Theragnostic platforms combine biosensing, imaging, and therapeutic modulation to both sense analytes of interest while simultaneously allowing for treatment. Typical biosensing targets include neurotransmitters (i.e., DA, NE and SA) in a healthy CNS and inflammatory markers or disease specific hallmarks in a diseased or injured CNS (i.e., neurotransmitters or Aβ and tau respectively). Compared to a healthy CNS, a diseased/injured CNS displays several pathological features, including demyelinated neurons, increased protein aggregation, macrophage infiltration, decreased BBB integrity, and necrosis that serve as therapeutic targets while simultaneously providing sensing targets, thus lending itself to theragnostic applications of nanomaterials. Scaffold-based delivery is adopted from Yang et al. Reproduced with permission [81].

performed to support clinical diagnoses. For example, abnormal amyloid plaques and p-tau accumulation-induced neurofibrillary tangles (NFT) are diagnostic cues of AD in clinics.

However, conventional imaging techniques cannot detect neurological disorders in their earliest stages due to low spatial resolution and the difficulties of diagnostic probes penetrating the BBB [7]. Based on the increasing advancement of nanotechnology, it is now possible to overcome the obstacles outlined above in the early diagnosis of neurological diseases. To date, various diagnostic strategies incorporating nanotechnology have been reported to facilitate the early and sensitive detection of neurological disorders biomarkers [8]. To achieve satisfactory spatial resolution, magnetic nanoparticles and manganese oxide nanoparticles have been developed as contrast agents for enhanced MRI [9,10]. Furthermore, plasmonic nanomaterials, such as gold nanoparticles (AuNPs), silver nanoparticles (AgNPs), and their hybrid structures, have been widely used in imaging and biosensing to enhance sensitivity and specificity [11]. Gold nanostructures with versatile surface modifications, biocompatibility, and unique optical properties, such as metal-enhanced fluorescence (MEF), are the most studied nanomaterials in medical applications [12-14]. Carbon-based nanomaterials, including graphene and carbon nanotubes (CNTs), alongside their derivatives, have different physical and chemical properties and provide several applications in diagnostics [15]. Other interesting nanocomposites, such as quantum dots (QDs) [16], upconversion nanoparticles (UCNPs) [17], metal-organic frameworks (MOFs) [18], nanofibers, and nanoarrays have been investigated with promising diagnostic potentials in neurological applications. Herein, the recent progress of nanotechnology-assisted diagnostics will be discussed in the following sections.

2.2. Injuries and Inflammation in the Central Nervous System (CNS)

The CNS comprises the brain and the spinal cord, which are essential for speech, spatial processing, auditory processing, and motor functions. The most common injuries to the CNS include

stroke, traumatic brain injury (TBI), and spinal cord injury (SCI) [19,20]. While each injury is distinct, each disorder results in varying degrees of neural inflammation, in which reactive microglial cells are heavily implicated [21,22]. While other cell types are involved in propagating inflammation, microglia are directly modulating the inflammatory state by releasing pro-inflammatory or anti-inflammatory cytokines or chemokines [23]. The activation of microglia has been hypothesized to follow the phenotypic changes observed in macrophages, that is M1 classical or proinflammatory and M2 anti-inflammatory macrophages, following CNS injury or disease [24-26]. While this phenotypic classification can be interpreted as over-simplistic, the therapeutic strategy of converting microglia to an anti-inflammatory state remains justifiable. In an activated state, microglia release apoptosis-inducing cytokines (e.g., interleukin 1 beta [IL-1b], interleukin 6 [IL-6], tumor necrosis factor-alpha [TNF-a]) and chemokines (MCP-1), which can exacerbate neuronal loss and reduce functional outcomes [27].

As a therapeutic approach for treating neural inflammation and preventing neuronal damage, researchers aim to fundamentally understand and convert microglial phenotypes from pro-inflammatory to anti-inflammatory. Moreover, while many immunosuppressive drugs have been well-established for global anti-inflammation, their bioavailability, efficacy, solubility, and delivery can be improved by utilizing functional inorganic nanomaterials [28,29]. Biological barriers to efficient drug delivery, such as the low permeability of cellular lipid membranes or the highly regulated BBB, can be overcome by introducing nanomaterials for efficient cellular uptake and receptor-targeting capabilities [30]. Moreover, by leveraging the physical properties of nanomaterials, many of them can be utilized to impart imaging and diagnostic modalities, thereby lending themselves to theragnostic applications [31,32]. Therefore, for modulating the inflammatory state of the brain during neural disorders and given that microglia serve a primary role in many brain functions, this review will first focus on microglia-mediated inflammation and using functional inorganic nanomaterials to theragnostically alter phenotype towards an anti-inflammatory state.

While inflammation underpins the progression of neural disorders, this review will also cover functional inorganic nanomaterials for treating CNS injuries such as stroke, TBI, and SCI, which have similarities with respect to pathology and tissue damage. Nonetheless, an embolism often causes ischemic stroke by impeding blood flow and, thus, oxygen transfer to a specific brain region, whereas hemorrhagic stroke is caused by a damaged or ruptured blood vessel, resulting in internal bleeding into the brain. Both types of strokes cause a lesion site of neural damage [33,34]. Similarly, TBI and SCI result in lesion sites in the brain or spinal cord, respectively, due to an external force or trauma. Challenges in treating stroke, TBI, and SCI, include modulating microglial inflammation, as previously mentioned, but also include the ability to therapeutically regenerate neural tissue in the hopes of promoting functional recovery [35]. Here, we will also cover functional inorganic nanomaterials as tools to both understand and facilitate the generation of neurons for potential CNS therapies. Simultaneously, imaging and diagnostics represent significant hurdles encompassing theragnostics of CNS injuries and inflammation. Brain imaging through methods such as magnetic resonance imaging (MRI), computed tomography (CT) scans, and positron emission tomography (PET) [36], have drawbacks, including resolution (MRI & CT), or longevity (PET) that can be overcome with nanomaterials.

2.3. Neurodegenerative Brain Conditions

Neurodegeneration can be classified as the chronic loss of neuronal tissue associated with prolonged CNS inflammation [37-39]. Therefore, this review will also cover neurodegeneration under the umbrella of neural disorders and functional nanomaterials for their theragnostic application potential. The most common neurodegenerative diseases (NDD) include Alzheimer's disease (AD) and Parkinson's disease (PD). Alzheimer's disease is characterized by two main pathological hallmarks, which also serve as targets for theragnostic applications. First, amyloid precursor protein is incorrectly cleaved to predominantly yield amyloid-β peptide (Aβ) 42, which spreads throughout the brain by seeding and extracellularly aggregating to form cytotoxic oligomers and plaques [40,41]. While not directly correlated, the level of amyloid burden in combination with cognitive deterioration is generally used as an indicator of AD progression. Based on this, amyloid protein has been investigated as a biomarker for the early diagnosis of Alzheimer's disease and as a therapeutic target [42,43]. Nanomaterials and functional nanobiosensors have been used to enhance the clearance and detection of AD biomarkers as more effective theragnostic tools, which this review will examine [FIGURE 2**A, B**]. Nonetheless, due to the lack of clinical success of amyloid-targeting therapeutics, another popular AD biomarker is phosphorylated tau (p-tau), a late-stage pathological hallmark of AD which presents itself through the intracellular aggregation of hyperphosphorylated tau protein [44]. The second NDD this review will partially cover is PD. In PD, dopaminergic neurons selectively undergo apoptosis leading to motor deficits [45]. There are several potential known causes for Parkinson's including genetic disposition, environmental toxins like heavy metals, chronic exposure to trauma, etc. Therapeutic and diagnostic approaches have been reported to restore dopaminergic neurons, enhance overall brain dopamine (DA) concentrations, and regenerate neuronal tissue [46-48]. Overall, several significant challenges exist in treating neurodegenerative brain diseases, which may be distinct from treating neuroinflammation itself. First, the underlying cause of AD and PD remains unknown, which may require more sensitive diagnostic tools to understand disease progression and degenerative neuronal processes which are covered in this review. Second, protein misfolding is commonly observed in neurodegenerative diseases and may require nanomaterials to inhibit protein aggregation and subsequent oligomer formation to, prevent further cytotoxicity.

3. Dimensionality Of Inorganic Nanomaterials For Neural Therapeutic Applications

3.1. 0D Nanomaterials

Zero-dimensional nanomaterials are particles with diameters ranging from 1 nm to 100 nm [49]. Over the last several decades, nanoparticles have been utilized for a plethora of biomedical applications, ranging from drug delivery to bioimaging. Nanoparticles can be comprised of various chemical compositions but are easily grouped into organic or inorganic materials. While the focus of this review is centered around inorganic nanomaterials, a brief overview of 0D organic particles will briefly be provided. Liposomal nanoparticles, comprised of amphiphilic lipids that self-assemble to form spherical organic nanoparticles, have seen the most clinical success due to their ability to encapsulate hydrophobic drugs, improve biocompatibility, and biodegradability [50]. Liposomal nanoparticle formulations have been FDA approved for chemotherapeutic agents to lower dosage requirements, thereby improving tolerability and attenuating non-specific cell death for the patient [51]. Nanoparticles can take on multiple capabilities and hybrid compositions in a research setting. To this end, additional types of organic nanoparticles, such as those comprised of biopolymers or peptides, have the main advantage of being biodegradable. For

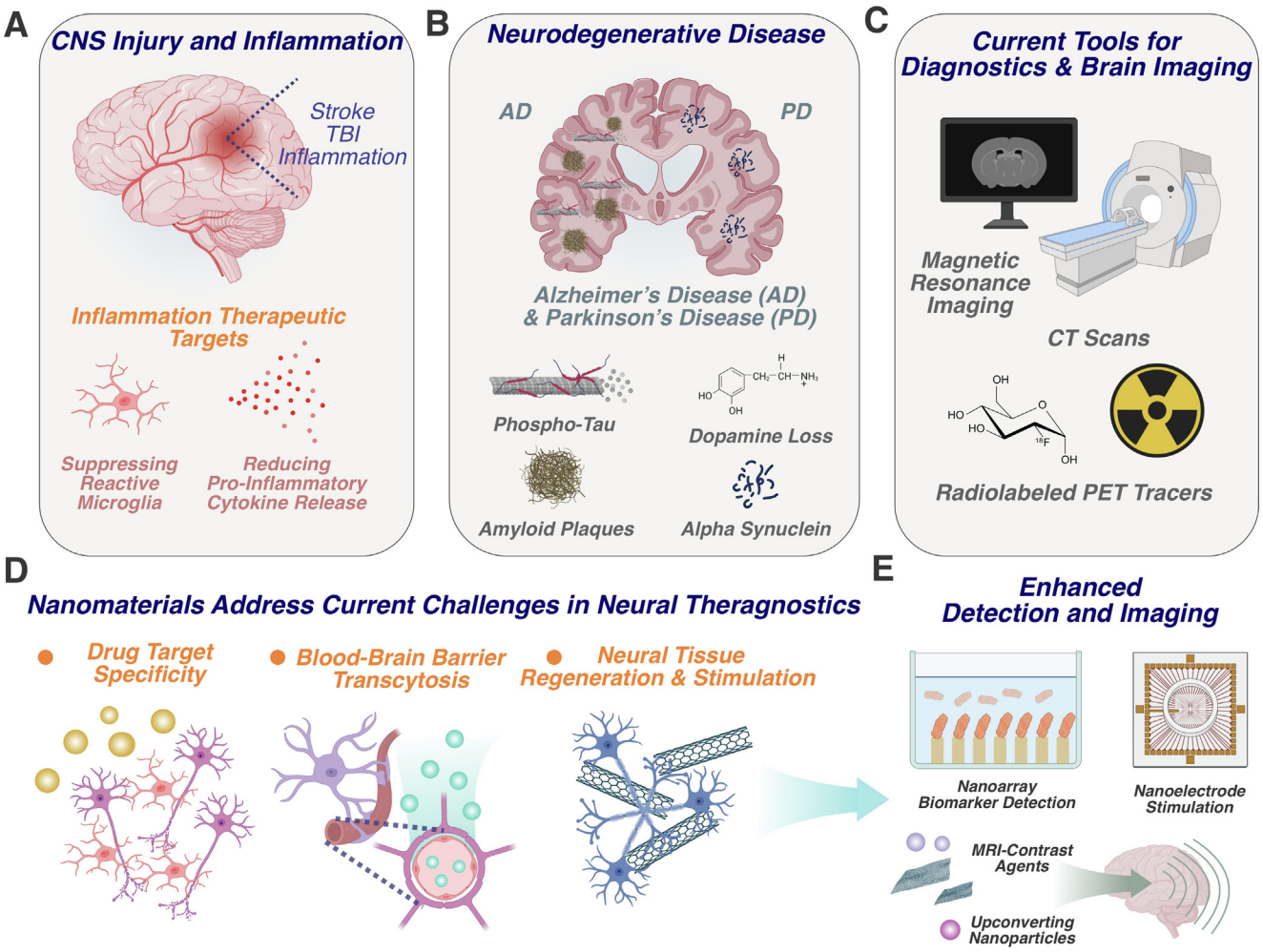

Figure 2. Implementation of nanomaterials to overcome challenges associated with neural disorders. Various conditions of the CNS can be modulated utilizing nanomaterials while simultaneously imparting imaging and sensing functionality for a dual modal approach. (A) Neural inflammation is a hallmark of CNS injury, as well as being present in neurodegenerative diseases. Often, approaches that modulate cytokine release in microglia and attempt to polarize them towards an anti-inflammatory state are implemented. (B) AD and PD are characterized by NFT, p-tau, Aβ accumulation, DA loss, and α-synuclein aggregates. (C) Inorganic materials can serve as MRI contrast agents or can have imaging capabilities by functionalizing contrast agents to their surface. (D) Various nanomaterial compositions have been implemented in theragnostic applications with a commonality being to target specific cell lineages, safely pass through the BBB, stimulating neural tissue for probing mechanisms or for regeneration, and (E) detecting/imaging functionality.

example, polymeric nanoparticles synthesized from poly-L-lactic acid (PLA), poly(lactic-*co*-glycolic acid) (PLGA), or poly-L-lysine (PLL) can be loaded with small molecule or growth factor therapeutics to provide a biodegradable drug delivery platform [52,53]. However, without additional surface modification, these nanoparticles have burst drug-release kinetics that may not be favorable for biomedical applications requiring sustained or on-demand drug delivery. Additional surface modification or doping methods can provide external control of drug delivery. For example, several photolytic mechanisms of drug release, wherein light stimulation induces bond cleavage, can prevent non-specific drug release within *in vivo* systems [54]. One drawback of photolytic mechanisms present in nanoparticle systems is that visible light penetrance through the skin, or thick tissue is very poor, thereby limiting potential biomedical applications. As a solution, researchers have shifted towards utilizing inorganic nanoparticles and designed upconversion nanoparticles, which utilize high-wavelength excitation (i.e., near-infrared [980 nm, 808 nm]) to emit visible light to allow for deeper tissue penetration. UCNPs are primarily comprised of metal lanthanides (i.e., ytterbium, neodymium, erbium, and thulium) that have the unique property of undergoing anti-stoke shifts, thus resulting in the emission of light with a lower wavelength than excitation [55]. Overall, UNCPs hold great potential for bioimaging and stimuli-responsive drug release.

Other inorganic nanoparticles for drug delivery include well-established gold nanoparticles, which have underpinned many zero-dimensional nanomaterial approaches for drug delivery, and magnetic nanoparticles (MNPs). Gold nanoparticles have several advantages that make them ideal. First, gold is inert in biological systems, and gold nanoparticles have been FDA-approved [56]. Second, the gold-thiol bond is very strong and renders gold nanoparticle surface chemistry easily adaptable to conjugate small molecules, peptides, and proteins. Similarly, MNPs are readily used for drug delivery and are commonly employed in conjunction with magnetic hyperthermia for cancer therapy [57]. The common composition of MNPs included an iron oxide (Fe_3O_4) crystal doped with either zinc, manganese, cobalt, or nickel [FIGURE 3**A**].

3.2. 1D Nanomaterials

Nanotubes, nanowires, and nanofibers are some of the most commonly utilized 1D nanomaterials that demonstrate unique structural advantages, such as their extraordinary length, flexibility, mechanical strength, and tunable optical properties. Due to

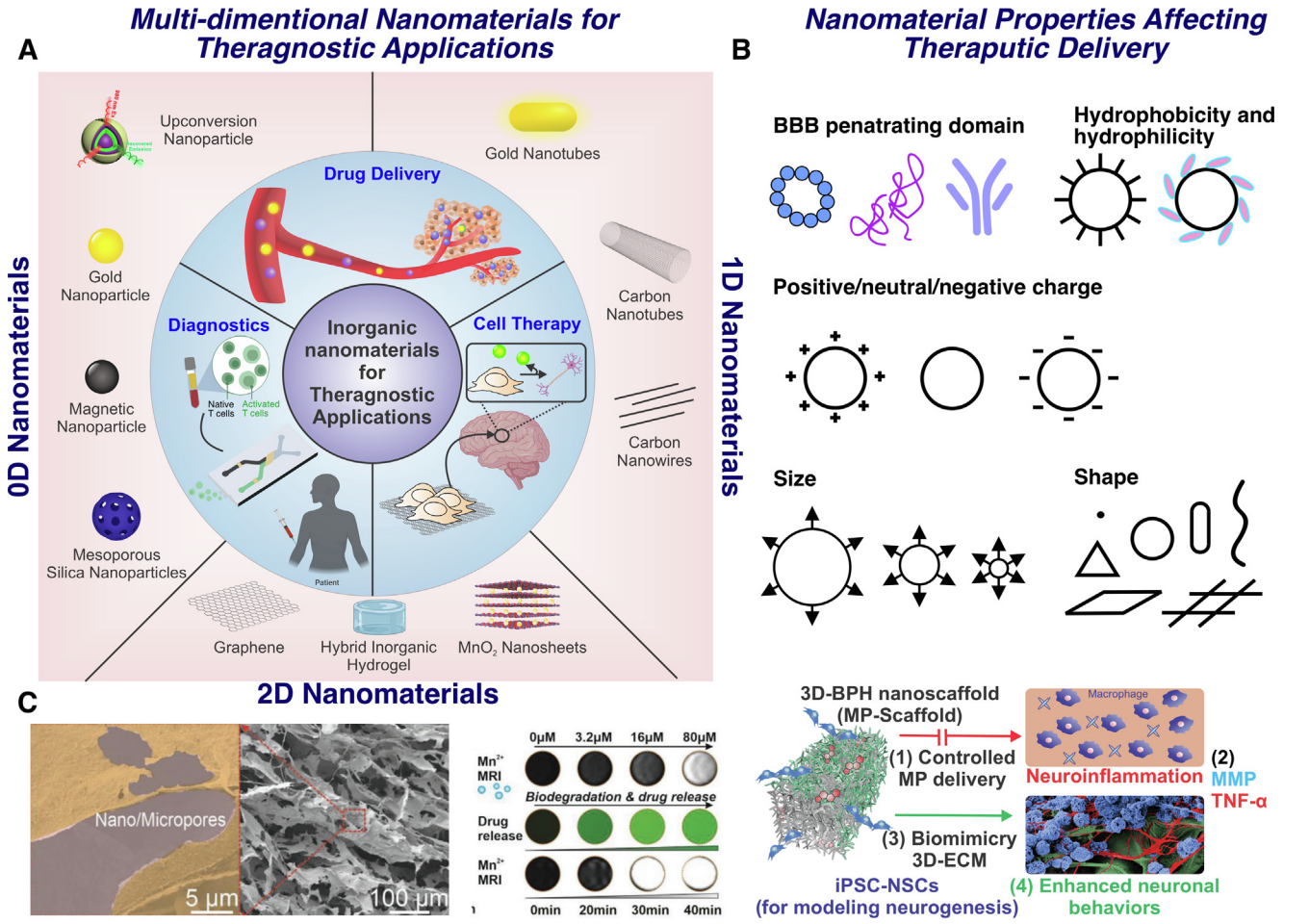

Figure 3. Usage of multidimensional nanomaterials for theragnostic applications in the CNS and factors that contribute to their functionality. (A) Overview and applications of Theragnostic inorganic nanomaterials utilized in neural disorders and probing neural processes. Three major classifications of materials (0D, 1D, and 2D) will be discussed in detail due to their multifunctionality. (B) Various aspects that control functionality of 0-2D materials. (C) Theragnostic platform that combines imaging (i.e., MRI) with small molecule to enhance neuronal differentiation while mitigating neuroinflammatory conditions. Reproduced with permission [81].

their unique mechanical properties, 1D nanomaterials can be physically or chemically manipulated to suit various biomedical needs. Moreover, by tailoring the optical properties of these materials, one can easily tune the absorbance and create hot spots suitable for generating heat and sensing, respectively, thereby lending themselves to various theragnostic applications. For example, multi-functionalized 1D gold nanorods (AuNRs) can be utilized to integrate bioimaging and phototherapy into a single platform with diagnostic and therapeutic functionality. Morales-Zavala et al. developed an AuNR-based therapeutic peptide delivery system that can also be used for *in vivo* microcomputed tomography (micro-CT) imaging. In this design, polyethylene glycol (PEG) conjugated AuNRs were functionalized with the peptides Ang2 (which is a targeting moiety to the CNS) and D1 (which can bind to Aβ peptides and inhibit their aggregation). After a single treatment utilizing the AuNRs-D1/Ang2, there was significant inhibition in Aβ aggregation and a significant decrease in their cytotoxic effect. Further *in vivo* studies using an AD transgenic mouse model showed a decrease in the amyloid load and inflammatory markers in the brain after a recurrent treatment for one month with AuNRs-D1/Ang2. This AuNR-based nanosystem design exhibits promising properties for neuro-theragnostics in AD [58].

Another example of 1D nanomaterials includes CNTs, cylindrical allotropic forms of carbon that consist of rolled-up sheets of single-layer carbon atoms in a regular hexagonal lattice. Carbon nanotubes were first discovered by Lijima et al. [59] and have been thoroughly studied and developed ever since. While the diameter of CNTs varies from 0.4 to 2 nm for single-wall carbon nanotubes (SWCNTs) and from 1.4 to 100 nm for multi-wall carbon nanotubes (MWCNTs), the length of CNTs varies and has been expanded with the longest single carbon tube being 550 mm reported by Zhang et al. The outstanding properties of CNTs, such as ultra-light weight, high flexibility, large surface area, high storage capacity, excellent chemical and thermal stability, and extreme electronic properties, make them a raising and useful tool with great potential in neurobiological applications, such as treating neurological disorders including AD, PD, and ischemic stroke [FIGURE 3] [60-62].

In this vein, the unique physical properties of CNTs have been attracting people's attention in the area of biomedical imaging. The 1D semi-conducting SWCNTs exhibit a narrow band gap that allows fluorescence emission in the near-infrared (NIR) regions (700 nm–1400 nm) [63-65]. Also, CNTs serve as an excellent contrast agent in photoacoustic imaging due to their dark appearance and strong absorbance in the NIR region [66]. Moreover, SWCNTs possess enhanced Raman scattering due to their strong plasmatic resonance and large scattering cross-section [67]. Additionally, CNTs can be combined with metal nanoparticles or other moieties for enhanced MRI [68], PET [68], and single photon emission computed tomography [69].

Carbon nanotubes hold great potential in theragnostic nanomedicine due to their inherent optical, electrical, and plasmonic features for biosensing and bioimaging applications and the ease of integrating diagnostic agents to monitor the effectiveness of pharmacological treatment at the cellular and molecular levels. Diagnostic agents commonly used in theragnostic nanomedicine and suitable to be combined with CNTs in *in vivo* and *ex vivo* assessments include fluorescent probes for optical imaging, paramagnetic metals for magnetic resonance imaging, and radionuclides for nuclear imaging [70]. Although the reported application of a theragnostic CNT-based platform in neural disorders and neurogenic cell therapy is still limited at this time, it certainly holds great potential in providing combined biosensing/imaging and therapeutic activity for treating neurodegenerative diseases and CNS injuries.

3.3. 2D Nanomaterials

Functional 2D inorganic nanomaterials have been utilized for neural stimulation, neural interfaces for cellular therapy, and enhanced CNS treatment of inflammation and injury. Two-dimensional nanomaterials can provide excellent mechanical and electrical properties (e.g., conductivity) due to strong in-plane nanosheet bonding and can encompass compositions such as metal oxides, and transition metal dichalcogenides, MXenes, carbon-based materials, and more [71-74]. 2D nanomaterials, most notably graphene and graphene oxide (GO) derivatives, have superior electron carrier mobility and conductivity compared to conventional organic biomaterials or conductive polymers. They have been widely used in biomedical applications, specifically for neural disorders [FIGURE 3]. Graphene and GO derivatives are commonly integrated into brain electrodes to stimulate and record neural cells, thereby improving sensitivity through signal detection and reducing background noise [75,76]. Maintaining prolonged conductivity in a biological medium is a significant challenge, especially *in vivo,* where fibrosis reduces electrode or implant performance and therefore requires nanomaterials to enhance functionality. While many nanomaterial-modified electrodes or implants include graphene or carbon-based materials, black phosphorous nanosheets have been developed within an injectable strategy to wirelessly stimulate cultured neurons [77]. Furthermore, 2D inorganic nanomaterials have similar advantages to other nanomaterial dimensionalities in that a high surface area provides greater nanomaterial interaction with loaded therapeutics. Biocompatible 2D nanomaterials (i.e., non-toxic) are often chosen for drug delivery and therapeutic purposes. Inorganic or carbon-based nanomaterials, such as graphene and GO nanosheets, are frequently chosen for CNS applications such as spinal cord treatment, neuronal regeneration, and traumatic brain injury as these nanosheets do not generally exhibit negative short-term cytotoxicity [78-80].

Nonetheless, the long-term biodegradation and biodistribution of graphene-based nanomaterials for the treatment and imaging of neural processes remains unclear and is still heavily investigated [79]. To this end, researchers have investigated 2D inorganic nanomaterials (such as MnO_2 nanosheets) with the potential for theragnostic applications to address concerns for long-term effects on the CNS microenvironment. Interestingly, 2D-MnO_2 nanosheets can be degraded *in vitro* and *in vivo* through a redox reaction facilitated by cellular-secreted reductants such as ascorbic acid or glutathione. Furthermore, Mn^{2+} can serve as a T1 MRI contrast agent, which may lead to better diagnostic capabilities. Furthermore, 2D-MnO_2-based scaffolds have been developed to facilitate neuronal regeneration and deliver anti-inflammatory molecules after spinal cord injury [FIGURE 3**C**] [81,82]. The following sections will further expand upon the emerging uses of these two-dimensional nanomaterials and their potential and applications for treating CNS injury and imaging strategies.

3.4. Toxicity of Nanomaterials

Considerable efforts have been made to characterize the potential toxicity of nanomaterials both *in vitro* and *in vivo*. In some of these studies, results may differ due to the physiochemical properties of the material, the types of cells being targeted, and the dispersity of the nanomaterial. Despite this, an overview of the toxicity of the various nanomaterials described in this review will be provided, with more specific references provided where necessary. A comprehensive review of the effects of surface chemistry and structural changes on the toxicity of these materials is beyond the scope of this article. Despite this fact, TABLE 1 highlights materials that may have toxicity concerns.

Gold nanomaterials are among the most commonly used in biomedical research due to their biological inertness, optical properties, electrochemical electrical properties, and availability, and have been used as drug delivery agents, photothermal agents, radiotherapy dose enhancers, and tumor and antigen detection [83,84]. Before going further, it should be noted that the bioinert property that is often attributed to gold nanomaterials is true for larger gold nanomaterials (i.e.,10 nm). Gold nanoparticles smaller than 2 nm (i.e., gold nanoclusters), exhibit chemical reactivity, which might result in increased oxidative stress and mitochondrial damage, depending on the structure and surface ligands present on the gold cluster [85-88]. With this in mind, there have been several applications of gold nanomaterials that have undergone clinical trials, including AuroLase, a silica-gold nanoshell used for thermal ablation of cancer, and a spherical nucleic acid platform from Northwestern University that coats the surface of a gold nanoparticle for delivery to glioblastomas [89,90]. However, gold nanoparticles are not without their limitations, as is highlighted in the following review section, where they can influence cell viability and replication, produce oxidative stress, and thereby cause apoptosis in a cell-dependent manner [91]. Moreover, a typical theragnostic application of gold nanomaterials relies on utilizing AuNRs for detection, delivery, or enhanced imaging techniques. Typically, these materials are coated with the surfactant cetyltrimethylammonium bromide (CTAB). It has been demonstrated that CTAB-coated AuNRs exhibit cytotoxic effects that induce necrosis, thus causing the release of damage-associated molecular patterns (DAMPs) [92]. Subsequently, the release of DAMPs and CTAB-mediated activation of the STING pathway in neutrophils can initiate an innate immune response resulting in inflammation *in vivo*.

Another nanomaterial class widely considered safe for use *in vivo* is silicon-based materials and their oxides. Silicon and its material derivatives can be synthesized via bottom-up approaches to create solid or mesoporous structures. They are commonly utilized within the biomedical field in drug delivery, imaging, implants, and dental fillers [93-96]. Moreover, according to the FDA, silica is "generally recognized as safe" and is currently being utilized in clinical trials in the form of Cornell-dots for real-time imaging of nodal metastases [97]. However, much like gold, silica can interact with immunocompetent organisms to induce toxicity depending on their physiochemical properties. The usage and cytotoxicity of silica-based nanomaterials in biology and medicine have been extensively reviewed, in addition to their interactions with the immune system [98,99]. For example, crystalline silica nanoparticles have been shown to influence cell viability in murine macrophage cell lines (e.g., RAW 264.7) and patient cells with reticulum cell sarcoma (e.g., J774.1 cells) in a size and charge-dependent manner [99]. Similarly, this was accompanied by the activation of MAPK and NF-κB pathways, an increase in proinflammatory cytokines, and caspase-3 activation, ultimately resulting in

apoptosis. Similar studies on silicon-based nanomaterials highlight NLRP3 inflammasome activation, induction of oxidative stress, and Toll-like receptor (TLR) activation were also described in the same article.

Magnetic nanoparticles (MNPs), in the form of iron oxides and their derivatives, are another interesting class of nanomaterials that display unique cytotoxic behaviors. MNPs' toxicity, like that of previously discovered materials, is determined by their physiochemical properties, such as their capping ligand. They have been applied in a range of biological applications, including magnetofection, guided drug delivery, thermal ablation, and as dietary supplements for anemic individuals [100-102]. Iron oxide nanoparticles were FDA approved for the latter application [103]. Despite this, iron oxide nanoparticles can potentially cause ferroptosis, a type of iron-induced programmed cell death. Several mechanisms of ferroptosis have been reviewed for clinical drugs containing iron and free iron ions and their roles in iron metabolism, reactive oxygen species (ROS) metabolism, and activating MAPK pathways [104]. These processes are exacerbated in cardiomyocytes, where iron oxide nanoparticles have been demonstrated to induce oxidative stress, leading to ischemic cardiomyocytes, apoptosis, and necrosis in murine cardiac tissue [105]. Similarly, manganism is a form of manganese toxicity from excessive Mn levels in the CNS that may need to be considered and has also been reviewed [106]. However, since the normal concentration of Mn in the CNS is approximately 80 μM, it would require large amounts of Mn-containing nanomaterials, such as Mn-doped MNPs, to induce this phenomenon.

Upconversion nanoparticles (UCNPs) are synthesized using a low phonon energy host material. Of those identified in the literature, a $NaYF_4$ crystal is the most commonly utilized and has an appropriate amount of lanthanides doped in, replacing the yttrium in the host. Unlike the previous materials, UCNPs do not have any clinical trials or prior FDA approvals [107]. Thus, one of the major factors currently being studied is the toxicity of these particle systems. One of the main concerns when evaluating the toxicity of UCNPs is fluoride ion leaching. It has been suggested that fluoride is a developmental neurotoxicant, similar to lead and arsenic, that can reduce intelligence in children [108]. In a recent study, a NaYF4:Yb/Er nanoparticle was utilized to determine the amount of fluoride leaching present in these particles when coated with various polymers or other inorganic materials, such as silica. It was determined that there is both a concentration and surface-coating-dependent effect on cytotoxicity in HaCaT cells following the delivery of several UCNPs. Ultimately, ethylendiamine tetra (methylene phosphonate), poly(maleic anhydride-alt-1octadecene), and UCNPs with a thicker silica coating showed better viability and were correlated to less fluoride ion release [109]. However, this increased viability resulted in the reduced signal output from the UCNPs. Hence, further modifications must be conducted to increase cell viability without dampening the signal output.

Finally, carbon-based nanomaterials are unique, not only because of their mechanical and other previously described properties, but also due to the various forms the material can take on. This discussion will only consider graphene and CNTs, as their applications will be discussed later in this review. While these materials have been studied for years, they do not have any current FDA approvals. That being said, the toxicity of these materials is widely dependent on their structure and functionalization. For example, acid-functionalized SWCNTs have been found to exhibit concentration-dependent cytotoxicity, causing mitochondrial damage and inhibiting phagocytic activity when internalized by murine macrophages [110]. A study by Berio and coworkers concluded that certain types of MWCNTs did not promote cellular apoptosis, as made evident by a lack of caspase 3 and 7 activity. In contrast, Wang et al. demonstrated that acid-functionalized MWCNTs induced apoptosis via mitochondrial pathways [111,112]. Several other reviews dive into various mechanisms and studies that analyze graphene toxicity in depth [113,114].

To that end, the evidence shows that while some nanomaterials are considered more or less toxic than others, this highly depends on the particle's shape, size, and surface functionalization/coating. For example, negatively charged particles are generally less cytotoxic as they are less likely to disrupt cell membranes or be passivated with proteins *in vivo*. Similarly, PEGylating particles can camouflage them *in vivo*, reduce their toxicity, and evade immune cell detection. To this end, careful consideration should be made when deciding which material is suitable for which application.

4. Inorganic Nanomaterials For Therapeutic Modulation Of Neural Disorders

4.1. Reducing Microglial-Derived Inflammation

As neuroinflammation is strongly linked with neurodegenerative diseases and injury, numerous studies have been conducted to deliver small molecules to microglia to suppress inflammatory responses. One approach has been to functionalize the surface of AuNPs with flavonoids, such as quercetin, and deliver this system to microglia cells. Flavonoids are secondary plant metabolites known to have antiaging, neuroprotective, and anti-inflammation properties and have been suggested to be used as prophylactics to slow the progression of PD and AD [115,116]. However, the usage of quercetin is often hindered by its poor water solubility and instability under physiological conditions [117]. To address these limitations, Ozdal et al. stabilized quercetin onto the surface of citrate-coated AuNPs. After testing their effect on cell viability in BV-2 microglia, the scientists discovered that AuNP with adsorbed quercetin was substantially less toxic than free quercetin, allowing them to highlight the anti-inflammatory capabilities of their system *in vitro*. To accomplish this, BV-2 microglia were stimulated with lipopolysaccharide (LPS) to promote an inflammatory phenotype. Following the treatment of these cells, it was evident that the quercetin-adsorbed AuNP was more efficient in reducing proinflammatory enzymes (i.e., COX-2 and iNOS) at both the transcriptional and translational levels [118]. Another interesting approach to delivering small molecules to microglia has been to directly stabilize the surface of an AuNP with the molecule of interest. Xiao et al. reported an example in which they administered -lipoic acid (ALA) stabilized gold nanoclusters (AuNCs) to act as an antioxidant to reduce neuroinflammatory responses by polarizing microglia [88]. However, more in-depth descriptions have been reviewed previously for the polarized state of microglia and macrophages [119,120]. The two extremes when polarizing microglia are the proinflammatory M1 and anti-inflammatory M2 phenotypes. M1 microglia are activated by interferon-γ (IFN-γ) and LPS, an endotoxin usually found on bacteria capable of activating TLR4 [121,122], inducing neuroinflammation and impairing neurogenesis. Conversely, M2 microglia are activated by IL-4 and IL-13 and release IL-10, transforming growth factor-β (TGF-β), basic fibroblast growth factor (bFGF), and various other neuroprotective and neurodegenerative factors [123]. With this in mind, ALA was reduced to dihydrolipoic acid (DHLA) and utilized to stabilize the AuNCs before being delivered to LPS, and INF-γ stimulated BV-2 M1 microglia. The DHLA-AuNC was capable of reducing proinflammatory cytokines such as IL-1, IL-6, cluster of differentiation 86 (CD86), TNF-α, iNOS, and MHC-II, as assessed by quantitative polymerase chain reaction (qPCR) and an enzyme-linked immunosorbent assay (ELISA), while simultaneously shifting microglia to an M2 phenotype, as made evident by increased expression of

CD206 and Arg-1. Moreover, the DHLA-AuNC could scavenge ROS and prevent apoptosis by lipid peroxidation in this cell line. *Ex vivo* cultures using a brain slice model also highlighted the particle's ability to improve neurogenesis and reduce astrogliosis, which is typically observed following damage to the CNS and may inhibit axon regeneration [124].

In addition to targeting microglia to attenuate inflammatory responses associated with CNS injury and neuroinflammation, there has also been attention given to developing nanoparticle platforms that can cross the BBB and target specific cells, such as neurons, within the CNS. One such system was presented. In this article, the authors developed an AuNP coated with an exosome engineered to express a fusion protein composed of Lamp2b, an exosome membrane protein, and a rabies virus glycoprotein (RVG) [125]. This delivery method to neurons takes advantage of vesicle-mediated transcytosis as the RVG peptide has been shown to target acetylcholine (Ach) receptors on the BBB and preferentially targets neuronal cell types [126,127]. Although no small molecules were conjugated to the surface of the AuNP core, Transwell experiments to model the BBB and in vivo experiments following tail vein injection to mice demonstrated the targeted system's ability to localize and penetrate the BBB besides entering neurons. Zhang et al. also utilized gold nanoparticles to conjugate both a drug (i.e., 1,3-dimethylxanthine [THP]) to alleviate respiratory paralysis following SCI and a cell targeting peptide specific to neuronal cells (i.e., WGA) [128]. By taking advantage of the various functional groups present on the AuNP, the authors could conjugate the drug and target peptide by carboxyl to hydroxyl (EDC/DMAP) and carboxyl to amine (EDC/NHS) coupling. Furthermore, following the conjugations, the particle's surface possessed a strong negative charge, -35.6 mV, as evident by their zeta measurements. This, combined with the targeting peptide, may have increased the neuronal localization of their AuNP in the cervical spinal cord as negatively charged particles, regardless of shape and size, have been demonstrated to preferentially target excitable neurons as opposed to glial cells [129]. Through this work, the authors could deliver THP in C2Hx rats. They found that the drug conjugated to the AuNP improved respiratory effects for up to 7 days post-treatment. In contrast, the drug administered alone only had therapeutic effects for 3 hours.

While AuNPs are commonly used to deliver bioactive molecules to the CNS, several studies have used stimuli-responsive nanoparticles activated following NIR or external magnetic field irradiation, UCNPs, and MNPs respectively. It should also be noted that in addition to small molecule delivery, UCNPs have been widely utilized in optogenetics [130,131], and MNPs, specifically those coated with gold shells, have been utilized in single-cell mechanogenetics [132]. Liu et al. utilized a UCNP core coated with a zeolitic-imidazolate framework (ZIF-8)-photoacid (PA) + melatonin (MT) and a hydroxylamine-modified liposome containing a chimeric antigen receptor (CAR) of aldehyde-modified CTLA-4, referred to as CAR-M-UZPM, to deliver MT to microglia and inhibit M1 polarization [133]. A liposome was included to increase BBB permeability since MT alone has poor BBB permeability. In this work, it was determined that the UZPM alone was sufficient to bind to CD86, an M1 microglia surface marker, due to the presence of the CTLA-4 CAR, thereby providing an immunosuppressive effect. However, after irradiating the system with 980 nm NIR, the excited UCNP activates PA to generate a free proton that, in turn, causes the degradation of ZIF-8 to release MT to further promote the immunosuppressant effects in a rapid and spatiotemporal manner. This was validated by measuring the levels of IL-6 and TNF-α, as well as the levels of IL-4 and IL-10, after activating microglia with LPS and UCNP. Tomitaka et al. utilized a gold shell-coated MNP encapsulated within a liposome to create a trimodal image-guided drug delivery system to deliver tenofovir disoproxil fumarate to a human microglia cell line, CHME-5 [134]. The nanoparticles were trackable by MRI, magnetic particle imaging, and X-ray CT as positive contrast agents due to the incorporation of MNPs and gold. Moreover, by taking advantage of the system's magnetic properties, the authors demonstrated that their particle platform had a larger transmigration efficiency across their BBB model than just the liposomes alone.

4.2. Targeting Degenerative Brain Diseases

Oligonucleotides are often delivered to cells in an attempt to express or suppress a gene or multiple genes of interest. Commonly used oligonucleotides include plasmids (i.e., gene expression) as well as small interfering RNA (siRNA), microRNA (miRNA), and DNAzymes (i.e., gene suppression), the latter of which has been utilized more as a sensing probe within the CNS in more recent publications. Cui et al. demonstrated both the reduced neurotoxicity and enhanced transfection efficiency of plasmids to the hippocampus of C57 mice using a polymer-coated MNP [100]. This platform, which consists of a Fe_3O_4 core, was first encapsulated with PLGA and stabilized with an emulsifying lipid in a ratio of 10:2 (w/w). The surface was then treated with 3% branching polyethyleneimine (PEI-25kDa) to impart a positive charge, allowing the plasmid for green fluorescent protein (GFP) to interact with the particles electrostatically. Finally, an additional PEG layer was conjugated to the surface of the particle to increase the circulation half-life *in vivo*. After synthesizing and characterizing their system, the MNP-PLGA-PEI-PEG NPs viability and functional activity of the hippocampal neurons were determined via an MTT assay and by monitoring their calcium dynamics. These cells remained viable until approximately 100 ng Fe/mL was delivered, at which point the viability decreased to 80%. Moreover, the positively charged particles did not influence calcium dynamics until the concentration approached 100 ng Fe/mL, where the system elicited a transient and reversible increase in calcium ions. It was eventually concluded that negative or neutral particles coated with PEG could penetrate these neuronal cells without increasing calcium concentrations via magnetotransfection. While the plasmid contained the gene for GFP as a proof-of-concept experiment, this study demonstrated the viability and efficacy of such a platform in delivering larger oligonucleotides.

RNA interference (RNAi) is one of the most prominent ways for post-transcriptional gene silencing, in which researchers can use miRNA or siRNA to target multiple or individual RNA transcripts to block protein expression [135]. While RNAi mechanisms have been thoroughly described in the literature, a brief description will be provided. The siRNA pathway begins with exogenously delivered double-stranded RNA (dsRNA) being cleaved by the Dicer enzyme complex into siRNA. Next, the siRNA is loaded into the Argonaute 2 (AGO2) RNAi-induced silencing complex (RISC). The RNA duplex has perfect complementary pairing, and the AGO2 cleaves the sense, thus leaving behind the RISC containing the antisense strand. The siRNA guides the AGO2 to cleave the target mRNA catalytically. On the other hand, the miRNA pathway utilizes endogenous miRNA transcripts that are transcribed and processed to produce precursor miRNAs. The precursor miRNAs are exported by exporting 5 to the nucleus, which can bind to the Dicer enzyme complex and be loaded into the AGO2-RISC complex. Compared to siRNA, miRNA requires imperfect complementary pairing to cleave mRNA, resulting in various mRNA transcripts that can be targeted [136].

With this framework in mind, RNAi technology is one of the most prominent tools for delivering biological therapeutics. For example, Liu et al. demonstrated the ability to co-delivery siRNA and small molecules that are adsorbed or directly conjugated to the surface of a 15 nm AuNP to treat PD. In this study, curcumin

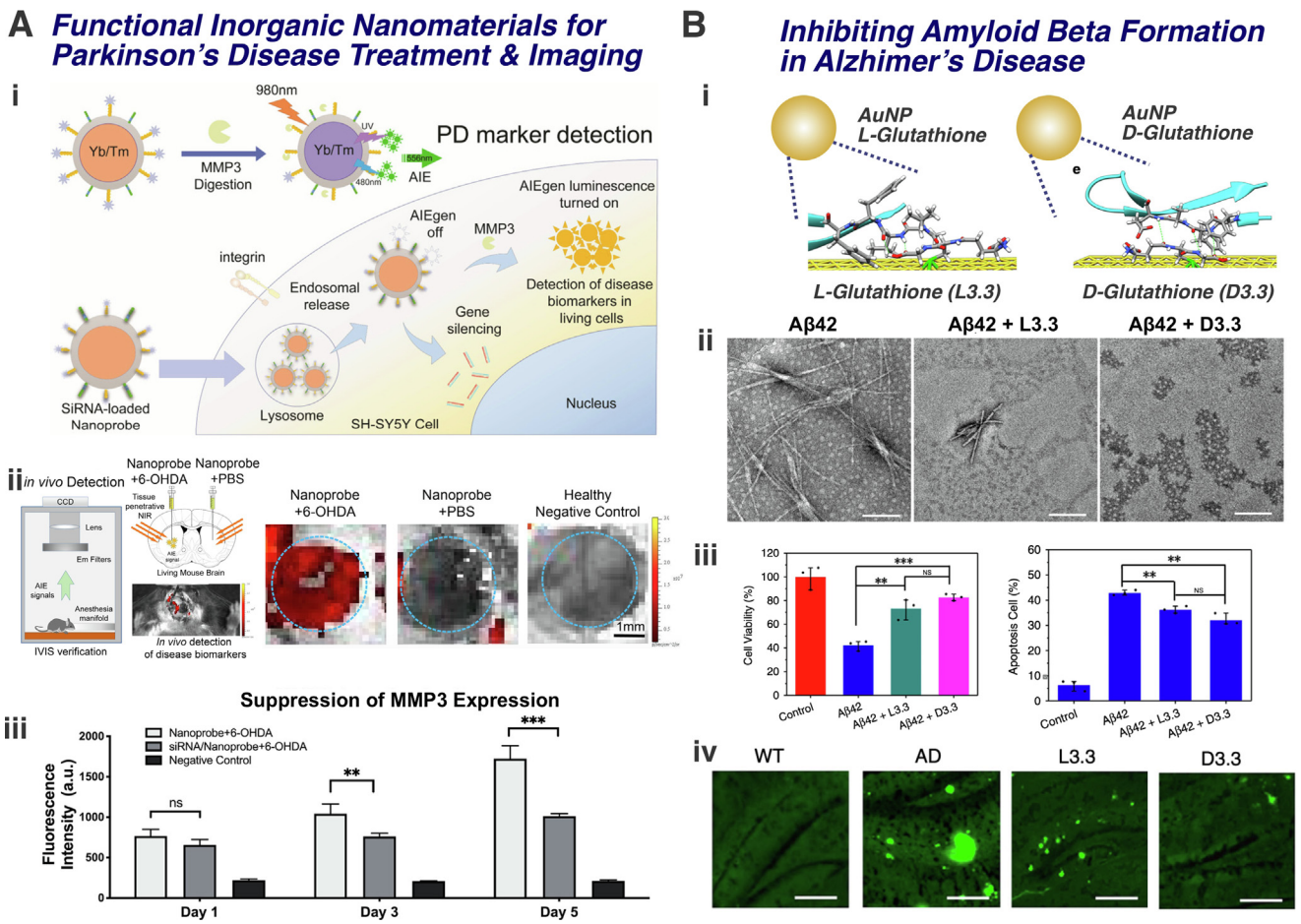

Figure 4. Therapeutic usage of nanomaterials in the treatment of PD and AD. (A) i) Design rationale of the UCNP-Peptide-AIEge nanoprobe for the detection and inhibition of biomarkers in PD models; ii) *in vivo* detection of MMP3 activity and imaging the UCNP-peptide-AIEgen nanoprobe in the striatum of PD mouse model 3 days after 6-OHDA injection with the IVIS; iii) quantitative results of the MMP3-triggered AIE signals in the stressed SH-SY5Y cells after the treatment of nanoprobes or siRNA-loaded nanoprobes. The intensity of MMP3-triggered AIE signals was significantly lower in the SH-SY5Y cells treated with MMP3 siRNA-loaded nanoprobes (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$; $n = 9$). (B) i) Most stable conformation of L- and D- glutathione coating the (111) surface of AuNPs in the presence of Aβ17-36; ii) TEM image of Aβ42 in the absence of and presence of L- and D-GSH coated AuNPs respectively; iii) cell viability and presence of apoptotic cells following delivery of Aβ42 with and without L- and D-GSH coated AuNPs; iv) immunofluorescence of Aβ in the hippocampus of WT, AD, and AD mice treated with L- and D- GSH coated AuNPs. Reproduced with permission [141,148].

derivatives (i.e., B6-PCB-S curcumin [BPC] and MA-PCB-S-curcumin [MPC]) were utilized in combination with siRNA for the α-synuclein gene (SNCA) [137]. These curcumin derivatives, BPC and MPC, respectively, are curcumin molecules conjugated to a B6 peptide (CGHKAKGPRK), that has been demonstrated to guide nanoparticles to target brain tissue on the BBB, and mazindol, which recognizes the dopamine transporter on dopaminergic neurons [138,139]. The B6 peptide has been utilized in previous studies as a transferrin substitute as it is more stable than transferrin, does not elicit immunological responses, and can cause nanoparticles to accumulate in brain capillary endothelial cells via clathrin-mediated endocytosis following binding to transferrin receptors on the BBB [139,140]. The curcumin derivatives were conjugated to the gold particle using a ROS-sensitive -thioester bond, which is cleavable in the presence of high ROS in the particle's local microenvironment, as seen in Parkinson's disease-derived dopaminergic neurons, to allow for stimuli-responsive release of the small molecule. Moreover, this functionalization imparted a positive charge on the surface of the gold particle that allowed siRNA targeting SNCA (siSNCA) to electrostatically adsorb onto the surface of the particles. It was found, through a combination of immunostaining and Western blot, that these particles can reduce the amount of α-synuclein protein aggregates in SH-SY5Y cells by reducing the number of RNA transcripts and, subsequently, the protein for α-synuclein. Finally, the authors tested the efficacy of this system *in vivo* following intravenous injection into C57BL/6 mice every 3 days over a 10-day period. Behavioral tests using an open-field experiment highlighted that treated PD mice had improved motor behavior as they crossed more central fields, had longer travel distances with shorter rest times, and had more rapid speeds relative to untreated mice. Also, the treated PD mice had improved grasp abilities compared to untreated PD mice. Similarly, there were pathological changes in the treated PD mice, such as decreased α-synuclein in tyrosine hydroxylase dopaminergic neurons.

Li et al. demonstrated a theragnostic approach to detect metalloproteinase 3 (MMP3) activity in inflammatory SH-SY5Y cells while simultaneously developing siRNA specific to MMP3 (MMP3-siRNA) [FIGURE 4**A**] [141]. MMP3 is an established target in treating PD as it has been shown to mediate excessive digestion of tight junctions that may cause BBB dysfunction in the midbrains of PD patients [142]. This work combines UCNPs with aggregation-induced emission fluorogen (AIEgen) to monitor and regulate MMP3 activity. A NaYF4:Yb/Tm UCNP was synthesized and silica-coated to provide a mechanism of upconverting NIR to UV light, thus activating the AIEgen peptide upon cleavage by MMP3, and

MMP3-siRNA was later loaded onto the surface of the silica coating. After being activated by 980 nm NIR, the previously described UCNP generates 480 nm light, which can excite the cleaved products and cause them to release a 556 nm signal. This process is initiated when MMP3 is present, which causes the AIEgen to be cleaved and begin to aggregate. This platform was sensitive enough to detect 60 pM of MMP3 by detecting the 556 nm emission and can detect early stages of PD *in vitro* and *in vivo*. The siRNA loading took advantage of electrostatic interactions between the positively charged peptide (CKKRGD) domain on the AIEgen peptide and the negatively charged siRNA. Confocal imaging and post-image processing highlight that the AIEgen and MMP3 fluorescent signals overlap and that the detection of MMP3 by the nanoprobe is specific to the target. Moreover, when treated with this nanoprobe, there was a significant reduction in both MMP3 and α-synuclein mRNA in inflammatory SH-SY5Y cells.

Proteins and peptides are another class of biological therapeutics that have been delivered to cells of the CNS. However, this approach is less commonly utilized due to the difficulties associated with protein delivery, including i) intrinsic properties of the protein that prevent passage through cell membranes (i.e., high molecular weight and polarity), ii) targeting a protein to a specific cell to reduce off-target effects, iii) poor stability, which is further exacerbated by endosomal entrapment. Thus, while it may be difficult to design ideal nanocarriers capable of entering the CNS, protecting, and effectively delivering a protein, several studies have aimed to highlight and address specific aspects of this problem. Despite the uptake and endosomal escape limitations, the delivery of peptides and proteins has advantages over-delivering plasmid DNA (pDNA). For example, approximately 70% of gene therapy clinical trials rely on viral vectors (i.e., lentiviruses and adenoviruses) to deliver the genetic payload due to their high gene transfer efficiency [143]. Despite this, several limitations are involved in utilizing viral vectors, including immunogenicity, tumorigenicity, limited packaging capacity, and scalability [144]. Thus, utilizing nanomaterials to deliver a protein of interest can circumvent many limitations.

One example of protein delivery to the CNS relied on the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Gold platform being delivered via intracranial injection to edit metabotropic glutamate receptor 5 (mGluR5). This target that has been hypothesized to provide therapeutic relief to individuals suffering from autism-related disorders, such as fragile X syndrome (FXS) [145,146]. CRISPR-Gold was developed by the same group and was previously demonstrated to induce homologous directed repair in BFP-HEK cells, primary myoblasts, and in *mdx* mice [147]. This work demonstrated that the system could directly deliver the Cas9 ribonucleoprotein (RNP) by first conjugating DNA to an AuNP. Next, a donor DNA strand hybridizes with the DNA and is subsequently complexed with the Cas9 RNP to allow protein attachment to the surface of the AuNP. Finally, a cationic and endosomal disruptive polymer, PAsp(DET), is utilized to coat the surface of the crisper functionalized AuNP to facilitate endocytosis and promote endosomal escape. By utilizing this nonviral delivery vehicle, the authors could knock out *Grm5*, the gene for mGluR5, and perform gene editing in both Thy1-YFP and Ai9 mice. In the Thy1-YFP mice, yellow fluorescent protein (YFP) is only expressed in neurons, and the CRISPR-Gold platform was designed to target the 5' region of the YFP. Following stereotaxic injection, it was noted that there was approximately a 17% decreased in YFP^+ cells and a 34% decrease in the YFP expression levels. To confirm that CRISPR-Gold can target multiple genes, Ai9 mice were then utilized to delete the stop sequence for tdTomato, and it was again found that 10-15% of the cells in the treated hippocampus were $tdTomato^+$. Next, the authors moved towards a more clinically relevant model of FXS using *Fmr1* knockout mice and found a 40-50% reduction in both transcript and protein levels of mGluR5, which was confirmed via reverse transcription (RT)-qPCR and immunostaining. It was also noted that there was no evidence of an elevated immune response by measuring mRNA immune marker levels in microglia.

Studies have focused on using small peptides as stabilizing ligands on the surface of particles rather than depending on the delivery of large proteins. This is because large proteins can be difficult to deliver. In this approach, the peptide acts as a stabilizing agent as well as a therapeutic alternative for the cells to which it is delivered. Recently, Hou et al. explored how the enantioselectivity of GSH functionalized AuNPs influences the particle's ability to cross the BBB and the binding affinity towards extracellular Aβ plaques [FIGURE 4**B**] [148]. It is important to note that GSH is a commonly used tripeptide for crossing the BBB due to a large number of GSH solute-carrier transporters that allow for an influx to the CNS [149]. In this work, the authors wanted to determine how these chiral nanoparticles, stabilized with L- and D-GSH, would pass through the BBB following intravenous administration, inhibit aggregation of Aβ42, and ultimately rescue behavioral impairments in AD mice. To begin, a Thioflavin T (ThT) fluorescence assay was performed to monitor the chiral nanoparticle's ability to inhibit Aβ42 fibrillation when incubated together. Although slight, the D-GSH enantiomer was more efficient in preventing fibrillation, evident by a 60% and 63% decrease in the maximum ThT intensity relative to pure Aβ42. This was further validated by atomic force microscopy (AFM) measurements whereby the Aβ aggregates appear amorphous with no discernable fibrillation when incubated with the D-GSH stabilized AuNP. To explain their findings, the authors performed isothermal titration calorimetry and found the interaction between GSH is primarily dictated by H-bonding and electrostatic interactions and that the binding constant for the D-GSH enantiomer was approximately 2.5 times larger than L-GSH when interacting with Aβ42. *In vitro* experiments demonstrated that D-GSH stabilized AuNPs reduce apoptosis rates in the presence of Aβ42 from ~43% to ~32% in SH-SY5Y cells, and *in vivo* experiments highlight the ability of this particle to rescue memory impairments in AD model mice following IV injection.

It should be noted that targeted delivery is not limited to 0D nanomaterials and that 1D nanomaterials can leverage their large loading capacity to achieve similar results. To this end, Yang et al. identified the pharmacological and toxicological profiles of SWCNTs in 2010. Using Kunming mice as an *in vivo* animal model, they examined the SWCNTs accumulation in mice intestinal cells and demonstrated that lysosomes are the predominant target organelles following delivery but that mitochondria also take up SWCNTs following large dose treatments. Furthermore, they loaded Ach in SWCNTs through sonication and treated kainic acid-induced AD mice via gastric gavage. After the delivery of these SWCNTs, various behavioral and motor tests were carried out on both treated and untreated mice to compare their responses. For instance, the step-down test, shuttle-box test, and the Morris water maze test showed significant dose-dependent recovery on learning and memory ability of SWCNT-Ach treated AD mice group relative to the negative control group, free Ach group, and SWCNTs without payload group. The researchers found that single-walled carbon nanotubes (SWCNTs) are effective drug transporters because they can transfer Ach into the lysosomes of neurons, resulting in a beneficial therapeutic effect. Thus, SWCNTs prove to have great therapeutic potential in treating CNS diseases [150].

4.3. Treatment of Central Nervous System Injury

Carbon nanotubes are potential candidates for developing synthetic scaffolds for tissue engineering. Because of their physical properties, such as micro-range length, extreme mechanical

Table 1
A literature summary of inorganic nanomaterials for therapeutic modulation of neural disorders.

NMs	Size	Surface module	Application	Cell line	Therapeutics	NM functions	Ref.
0D NANOMATERIALS							
AuNCs	1.87 nm	DHLA	Stroke *in vitro/ex vivo*	Microglial cell BV2	DHLA	Microglial polarizing, neural regeneration	[88]
AuNPs	3.3 nm	L- and D-glutathione	AD *in vivo*	SH-SY5Y	AuNPs	Inhibit Aβ42 aggregation	[148]
AuNPs	10 nm	DBD, AD, NLS	Gene regulating *in vitro*	Hela	Synthetic transcription factors	Nucleus targeting, gene delivering	[156]
AuNPs	15 nm	Levodopa-quinone	PD *in vivo*	SH-SY5Y	Zwitterionic PCB, siSNCA	Switchable gene-chemical co-delivery	[137]
AuNPs	15 nm	PAsp (DET)	DMD *in vivo*	HEK293, hESCs, BMSCs, hiPSCs	Cas9 RNP, donor DNA	Delivery vehicle	[147]
AuNPs	38 nm	WGA-HRP	SCI *in vivo*		THP, DPCPX	Deliver drugs, bypassing the BBB	[128]
AuNPs	60 nm		Gene editing *in vivo*	YFP-HEK cells	Cas9, Cpf1 RNP	Nonviral delivery vehicle	[146]
AuNPs	105nm	RVG-exosome	BBB model *in vitro*	Astrocyte, bEnd.3		Transport cross BBB, targeted delivery	[125]
AuNPs, AgNPs*	27 nm, 53 nm	Quercetin	Inflammatory NDD *in vitro*	BV-2 microglia	Quercetin	Suppression of acute microglial activation	[118]
MENPs	30 nm	Glycerol mono-oleate	*Ex vivo/in vivo*	Thy1-GCaMP6 transgenic mice		Targeted delivery, magnetic field-induced brain stimulation	[157]
MNPs*	45 nm	PEG, HPA, WRPW, MPP	Induced neurons *in vitro*	Rat NSCs	Sox9, GFP	Gene delivery	[158]
USPIONs		PEG	AD	SH-SY5Y	USPIONs	Prevent Aβ aggregation	[159]
MSNs	80-120nm	APTMS	*In vitro*	Mouse fibroblasts	Ascl1, Brn2, Myt1l, ISX-9	Non-viral delivery	[160]
MSNs	110 ± 30 nm	TMA	DA neuron differentiation *in vitro*	iPSCs	pNurr1, siRex1	Non-viral carriers	[161]
MnO_2	120nm	Macrophage membrane	Acute ischemic stroke *in vivo*	M1 microglia	Fingolimod	Cargo release, reduce oxidative stress, promote M1 microglia transition	[162]
UCNPs*	57 nm	$NaYF_4$:Yb@SiO_2	PD *in vivo*	SH-SY5Y	MMP3-siRNA	Drug delivering, real-time imaging	[163]
UCNPs*	80 nm	$NaErF_4$@$NaYF_4$@$NaGdF_4$: Yb/Tm	*In vivo*	C57BL/6 J mice	Neuronal activation	Optogenetic activation of neurons	[164]
UCNPs*	40 nm	$NaYF_4$@$NaYF_4$:Yb/ Er@$NaYF_4$	Optogenetics *in vivo*		eNpHR	Optogenetic neural stimulation	[165]
UCNPs*	33-68 nm	$NaYbF_4$@ $NaYbF_4$: Tm@$NaYbF_4$@SiO_2	Drug-induced neuropathic disorders	DRG		Targeted delivery	[166]
UCNPs*	50 nm, 70 nm	$NaYF_4$:Yb/ Tm, ZIF-8, photoacid, PEG, CTLA-4	Inflammation-related depression *in vivo*	M1 microglia	MT	Photoresponsive drug delivery	[133]
UCNPs*	90 nm	$NaYF_4$:Yb /Tm@SiO_2, PAA	Optogenetics *in vivo*	DA neuron		NIR-stimulated optogenetics	[131]
UCNPs*	96.1 ± 6.6 nm	$NaYF_4$:Yb/ Tm@$NaYF_4$: Yb/Nd@ SiO_2, PAA		hiPSC-NSCs	Neurogenic factor RA	Spatiotemporally controlled drug release	[167]
$Gd_2(WO_4)_3$:Eu	270nm	Ethylene glycol	*In vivo*	SK-N-SH	Brain stimulation	Promote optogenetic neural control	[168]
1D NANOMATERIALS							
AuNRs*	12 nm/ 36 nm	SH-PEG-NH_2, SH-PEG-COOH	Cell differentiation *In vitro*	Rat fetal NSCs		Promote cell survival and ODC differentiation	[169]
AuNRs*	4 nm/ 68 nm	PEG, D1, Ang2	AD *in vivo/ex vivo*	bEnd.3 cell	AuNRs	Brain delivery, amyloid plaque attachment	[58]
Au/ SiNWs	50-150 nm/ 2-3 μm		Cell differentiation *in vitro*	Rat cortical astrocyte		Enable astrocytes differentiation	[170]
ZnO NWs	< 500 nm	PEI	*In vitro*	NTera2.D1		Promote neuronal growth	[171]
ZnO NWs	200-350nm		*In vitro*	NSPCs		Guide cortical minicolumns formation	[172]
CNTs	10-30 μm lengths	PEG	Cell differentiation *in vitro*	NSCs, PC12, HiN		Promote neurogenesis, maintain neuronal network activity	[173]
CNTs	20nm/ 200nm	Ammonium	*In vitro*	CHO		Gene delivery	[174]
CNTs		Sericin	Ischemic stroke *in vivo*	BMSCs	Cell therapy	Deliver BMSCs, promote neuronal differentiation	[155]
CNTs	60 nm-100nm/5 μm	Hydrocarbon outer layer	Focal cerebral ischemia *in vivo*	SVZ NPCs	Cell therapy	Cell delivery, promote neuronal differentiation	[152]

Table 1 (*continued*)

NMs	Size	Surface module	Application	Cell line	Therapeutics	NM functions	Ref.
CNTs	50-70 nm	RADA16 peptide	*In vitro*	Rat HiN		Promote neuronal electrical activity	[175]
CNTs	4-10 nm/ 0.5-1.5 μm	Amine	Ischemic brain damage *in vivo*			Protect neurons, maintain cell-cell interaction	[154]
SWCNTs		PEG	*In vitro*	HiN		Promote neurite outgrowth	[176]
SWCNTs	1.5nm	SA, SpA, BSA, cyt-c	*In vitro*	HeLa, NIH-3T3, HL60, Jurkat		Intracellular protein transporter	[177]
MWCNTs	d: 15-37 nm	PEGDA	*In vitro*	NSCs		Promote neurite outgrowth	[178]
MWCNTs	d: 20-35 nm	-COOH	*In vitro*	hBMSCs		Promote hBMSC neural differentiation	[179]
MWCNTs	100nm	HNE, PABS, EN	*In vitro*	HiN		Promote cell growth	[180]
NANOPLATFORMS							
CNT pattern		Laminin	*In vitro*	hNSCs		Control neuronal differentiation	[181]
Graphene-nanofiber	200–300 nm	Laminin	CNS diseases and injuries *in vitro*	NSCs, MSCs, iPSCs		Guiding stem cell differentiation into ODCs	[182]
SiNWs	0.13 μm/ 20 μm		Stem-cell neurogenesis *in vitro*	hfNSCs		Intracellular electrical stimulation	[183]
SiNWs	30 nm /1 μm		Neuronal differentiation *in vitro*	Ipsc-NPC		Promote neuronal differentiation	[184]
SiNWs	60 nm/ 3-5 μm		*In vitro*	HEK293T		Record electrical activities	[185]
SiNWs	d:200-250nm		*In vitro*	DRG		Modulate neuron excitability	[186]
Graphene-Au nanoarray		Cy5-labeled DNA	*In vitro*	hNSCs		Enhance and monitor stem cell differentiation	[187]
Au-nanocup array		rGO	*In vitro*	hNSCs, PC12		Enhance stem cell differentiation, in situ detection	[188]
AuNR array			*In vitro*	NSCs		Promote astrocytic differentiation	[189]
multi-architectural nanoarray	1-2 μm		*In vitro*	Murine NPCs		Promote astrocytic differentiation	[190]
HTlc film		$[Zn_{0.72}Al_{0.28}(OH)_2]$ $Br_{0.28}0.69H_2O$	*In vitro*			Promote astrocytic differentiation	[191]
Silica colloids substrate	3.5-80nm		AD *in vitro*		Nano-roughness	Modulate neuron-astrocyte interaction	[192]
GBN scaffold		PCL	BBB model *in vitro*			Enhance astrocytic differentiation	[193]

* Materials may have cytotoxicity concerns.

DBD, DNA binding domain; AD, activation domain; NLS, nuclear localization signal; DMD,Duchenne muscular dystrophy; RNP, ribonucleoprotein; PCB, poly(carboxybetaine); ESC, embryonic stem cell; iPSC, induced pluripotent stem cell; WGA-HRP, wheat germ agglutinin-horseradish peroxidase; DPCPX, 8-cyclopentyl-1,3-dipropylxanthine; MENPs, magneto-electric nanoparticles; NSC, neural stem cell; HPA, hairpin polyamide; MPP, mitochondrial processing peptidase; USPION, ultrasmall superparamagnetic iron oxide nanoparticle; MSN, mesoporous silica nanoparticle; TMA, trimethylamine; DRG, dorsal root ganglion; eNpHR, enhanced natronomonas halorhodopsin; PAA, poly (acrylic acid); PEI, polyethylenimine; NSPC, neural stem/progenitor cell; HiN, hippocampal neurons; CHO, Chinese hamster ovary cells; SA, streptavidin; SpA, streptavidin-protein A; BSA, bovine serum albumin; cyt-c, cytochrome c; HNE, 4-hydroxynonenal; PABS, poly-maminobenzene sulfonic acid; EN, ethylenediamine; rGO, reduced graphene oxide; HTlc, hydrotalcite-like compounds; GBN, graphene-based nanomaterials.

strength and conductivity, and their ability to interface neuronal circuits, synapses, and membranes, CNTs have extensively been applied in tissue repair and functional recovery after brain surgery damage [151]. Carbon nanotube technology is currently employed to develop devices that drive nerve tissue engineering, focusing on neuronal differentiation, growth, and nerve tissue repair. Moreover, CNTs used as scaffolds in brain tissues and neural cells have shown promising results, supporting the treatment strategy based on transferring stem cells containing scaffolds to damaged brain regions. In rats with induced stroke, protection of neurons and enhanced recovery of behavioral functions were observed for the rats pre-treated with amine-modified SWCNTs. Arslantunali et al. constructed a nerve conduit from poly (2-hydroxyethyl methacrylate) (pHEMA) that was loaded with MWCNTs. This pHEMA guide was more hydrophobic and more conductive than pristine pHEMA hydrogel when loaded with relatively high concentrations of MWCNTs.

Carbon nanotubes have also been extensively used to treat acute brain and spinal cord injuries. Moon et al. first demonstrated the ability to improve stem cell differentiation in rats with induced strokes using CNTs. The authors transplanted hydrophilic (HL) CNTs-impregnated subventricular zone neural progenitor cells (SVZ NPCs), hydrophobic (HP) CNTs-impregnated SVZ NPCs, and SVZ HPCs alone to stroke-damaged rats. Both HP CNT-SVZ NPC and HL CNT-SVZ NPC transplants indicated an increase in neuronal marker microtubule-associated protein 2 (MAP2) and a decrease in astroglia marker glial fibrillary acidic protein within the injury epicenter 8 weeks post-transplantation. Results also demonstrated that HP CNTs outperformed HL CNTs in efficiency regarding differentiating SVZ NPCs, improving rat behavior, and reducing infarct cyst volume and infarct cyst area, suggesting a promising role of CNTs in neural transplantation and regeneration [152]. Protection of neurons and enhanced recovery of behavioral functions were also observed in the rats pre-treated with amine-modified SWCNTs, as indicated by the low levels of apoptotic, angiogenic, and inflammatory markers [153]. Lee et al. showed that pretreating rats with amine-modified SWCNTs could protect neurons and enhance the recovery of behavioral functions in rats with induced stroke. Treated rats showed less tissue damage than controls and took longer to fall from a rotating rod, suggesting better motor

function recovery after injury. Low levels of apoptotic, angiogenic, and inflammation markers showed that amine-modified single-walled carbon nanotubes protected the brains of treated rats from ischemic injury [154]. Wang et al. recently developed an injectable, photoluminescent, carbon-nanotubes-doped sericin scaffold (CNTs-SS) with programmable shape-memory property to precisely match any irregularly shaped cavities in an ischemic stroke model mouse (middle cerebral artery occlusion, MCAO) for optimized delivery of bone marrow-derived mesenchymal stem cells (BMSCs) into the brain injury site and to promote neuron survival. Immunofluorescence staining revealed that 14 days post-implantation of the cell-carrying CNTs-SS, there was improved cell survival and increased cell migration out of the scaffold. Furthermore, infiltration into neighboring brain tissue was observed. Neuron-associated mRNA and protein expression levels were analyzed using western blot, immunofluorescence staining, and qPCR. Consistent with the highly elongated neuronal morphology with axon-like subcellular structures observed using scanning electron microscopy, neuron-specific Tuj1 levels and the number of Tuj1 positive cells were significantly increased. The hierarchical clustering analysis with the high-level expression of a set of 40 neuron-associated genes also indicates a CNTs-SS scaffold-induced differentiation towards neurons [155]. Several other studies that utilize inorganic materials for CNS treatment are highlighted in TABLE 1.

5. Inorganic Nanomaterial Platforms For Diagnostics Of Neural Disorders

5.1. Biomarker Detection and Imaging in Degenerative Brain Disease

Accurate and early diagnosis of neurodegenerative diseases in clinical settings is always greatly valued. To this end, a comprehensive understanding of disease-related biomarkers is the underpinning to facilitate precise diagnosis, improve therapies, and revolutionize drug discovery for neurodegenerative diseases. The abnormal alternations of many biomarkers are associated with degenerative brain disease. A variety of small molecules and protein-based biomarkers have been discovered to date, and this section will introduce the representative biomarkers in degenerative brain disease.

Neurotransmitters, including peptides, amino acids, monoamines, and purines, have been important small molecules associated with central CNS function [194,195]. Neurotransmitters perform as messengers in neural circuits, which are important for maintaining normal function within the brain. During the synaptic transmission process, neurotransmitters are secreted to transmit signals across synapses to receiving neurons or other non-neuronal cells to relay information. Dopamine (DA) is one of the most important neurotransmitters that controls people's motions, emotions, attention, consciousness, and other neural functions [196]. The progressive loss of dopaminergic neurons in the substantia nigra is one of the leading causes of PD [197-199]. Therefore, abnormal alternations of DA in different biological fluids are regarded as a pathological indication of PD incidence. Aside from PD, dysfunction in producing DA is highly related to HD. Epinephrine (EP) is another important neurotransmitter released by adrenal glands, belonging to a group of catecholamines. The level of EP is an important factor for monitoring and diagnosing some neurological disorders, such as sleeping problems, anxiety, depression, etc. [200]. In addition to DA and EP, other neurotransmitters, such as glutamate, Gamaaminobutyric acid, norepinephrine (NE), histamine, tyramine, and serotonin, have been identified as key chemical regulators within the CNS [201].

The pathogenesis of some neurological disorders remains unclear currently, but there are hypotheses elucidating several key proteins that may partially cause abnormalities within the CNS [202]. For instance, two histological hallmarks are used to describe AD patients' brains and are core biomarkers for routine screening and diagnosis of AD. These include Aβ deposits known as amyloid plaques and aggregates of P-tau known as NFTs [42,43]. In addition, Lewy bodies are derived from the accumulation of the protein α-synuclein in neurons and will further result in the progression of PD, which is the second most prevalent neurodegenerative disease [203]. The excess aggregation of α-synuclein will induce high toxicity in the brain and facilitate the incidence of PD. Therefore, alpha-synuclein is considered to be a significant biomarker and a primary predictor for the early stages of Parkinson's disease [204]. Even though there is a lack of medical treatments available for AD and PD patients, early detection would serve primarily as a neuroprotective intervention for slowing disease progression and increasing the patient's quality of life. Multiple Sclerosis (MS), a chronic inflammatory demyelinating disorder of the CNS, is characterized by the profound loss of myelin loss and increased inflammatory response with increased levels of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-10, in cerebrospinal fluid (CSF) and serum [205]. Besides neurodegenerative diseases, gliomas, which account for 60% of all malignant brain tumors, have been associated with overexpression of the transmembrane protein neuropilin-1 [198]. Currently, the diagnosis of the aforementioned neurological diseases relies on the clinical evaluation of manifestations of these disorders and cognitive testing with relevant imaging and blood examination [5]. However, the most significant barrier to early identification is posed by the extended prodromal time of the initial detectable symptoms as well as the limits of existing diagnostic techniques [6].

5.2. Neurotransmitter Detection in Neural Disorders

Given that the level of neurotransmitters is within a nanomolar range, it is highly desirable to develop sensitive and accurate techniques for examining complex biological samples. Due to their unique properties, nanomaterial-based biosensors featuring high sensitivity have been investigated [194,198,206,207]. Biosensing devices that can be used for real-time monitoring of neurotransmitter levels are vital for understanding the biochemical responses of certain neurological disorders [194]. However, the development of existing real-time detection techniques is still at an early stage. Most recently, Zhenan Bao's Group developed a tissue-mimicking sensor for real-time monitoring of neurotransmitters in vivo, which is termed "NeuroString" [208]. This fabricated device achieved multiplexed and multichannel sensing in the brain of behaving mice and has also been used to dynamically detect serotonin in the gut. NeuroString was fabricated with a complex of metal-complexed polyimide and nanoparticle/graphene network. To enhance the sensitivity of the biosensor, metal-oxide nanoparticles (i.e., Fe_3O_4 or NiO) were modified on the graphene network. The nanoparticle/graphene-based biosensor allows the seamless interface with CNS and gastrointestinal system and enables the real-time monitoring of important neurotransmitters in both tissues, which deepens the understanding of neural functions and brain-gut communication.

Metal-organic frameworks, mimicking natural enzymatic activity, stand out as attractive nanomaterials in biosensing with various advantages, such as a stable and porous structure, high surface area, and a flexible and adjustable design. Wang et al. developed a copper-dopped MOF nanocomposite for colorimetric detection of the neurotransmitter DA that demonstrated high sensitivity and selectivity [209]. The synthesized MOF substrate presented the high catalytic activity to oxidize 3,3′,5,5′-tetramethylbenzidine (TMB) in the presence of H_2O_2 and generated a blue product. The Cu-MOF was applied for DA detection based on

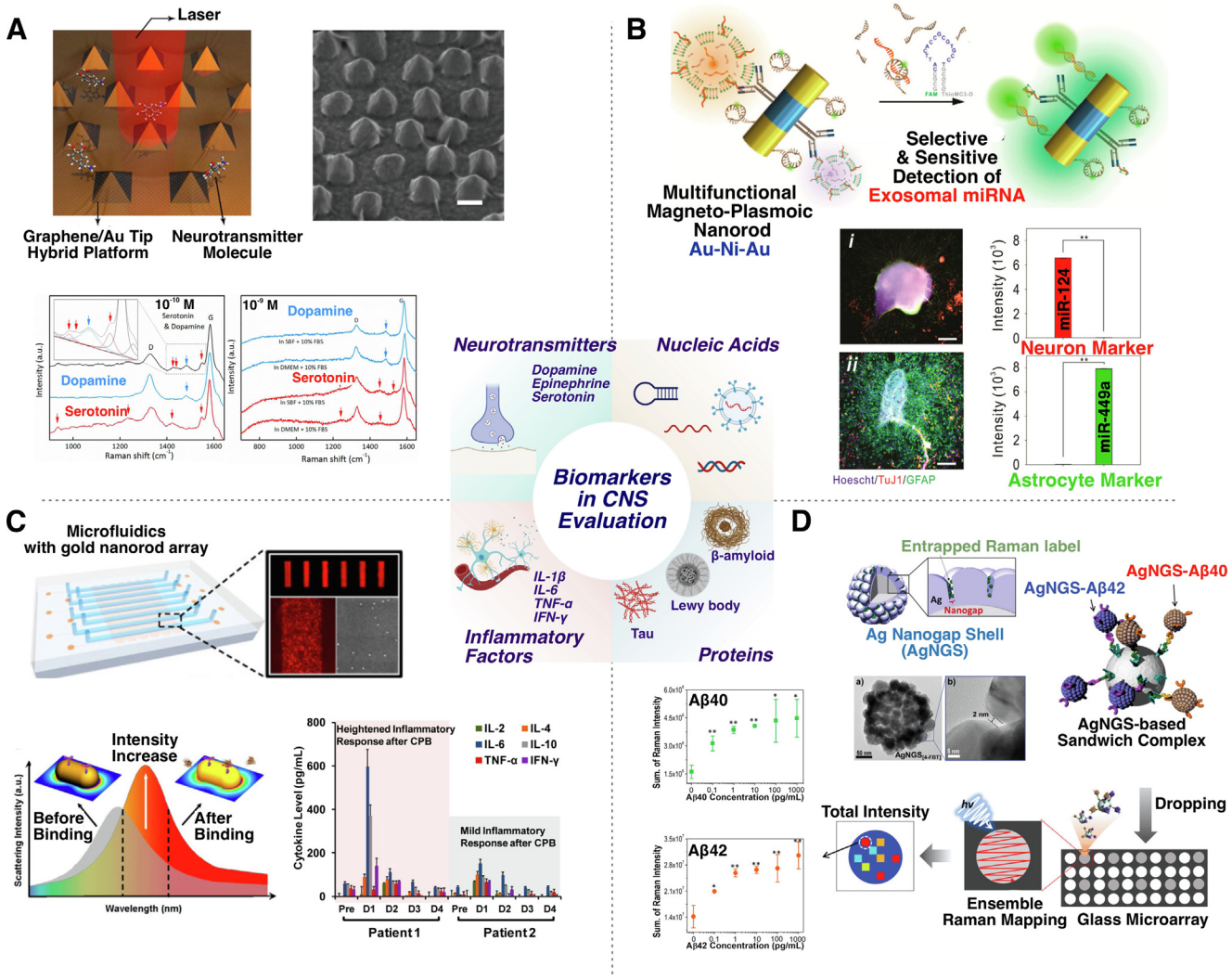

Figure 5. Sensing platforms used in the detection of hallmark biomarkers in the CNS. Biomarkers and detection in evaluating CNS conditions. (A) A graphene/Au tip hybrid structure-based SERS biosensor for simultaneous detection of dopamine and serotonin. (B) A nondestructive, selective, and sensitive characterization of stem cell differentiation by detecting exosomal miRNA using multifunctional magneto-plasmonic nanorods. (C) Multiplex serum cytokines detection on a nanoplasmonic array of AuNRs. (D) A Ag nanogap shell (AgNGSs) serving as a SERS nanoprobes for sensitive, selective and multiplexed detection of Aβ40 and Aβ42. Reproduced with permission [212,221,226,227].

the strong inhibitory effect of DA on the catalytical activity of the MOF. A smartphone platform was also incorporated with the developed biosensor to detect DA in human urine.

Simultaneous detection of DA and EP, using an electrochemical biosensor, was reported by Vinoth and coworkers [210]. The nanocomposite consisted of gold nanocrystals capped with graphene quantum dots (GQDs) as well as N-[3-(trimethoxysilyl) propyl] ethylenediamine (TMSPED) as a reducing agent. These composites were modified on a glassy carbon electrode for simultaneous detection of DA and EP, with a linear response from 5 nM - 2.1 μM for DA and 10 nM - 4.0 μM for EP, with detection limits of 5 nM and 10 nM respectively.

As described previously, inorganic nanoparticles can be combined with other materials to enhance sensing performance. In addition to the aforementioned analytical methods of colorimetry and electrochemistry, some metal nanoparticles and associated nanoarrays can significantly enhance Raman signals by orders of magnitude, which is known as surface-enhanced Raman spectroscopy (SERS). Moody et al. developed a SERS-based sensor for the rapid detection of seven neurotransmitters, including melatonin, serotonin, glutamate, dopamine, gamma-aminobutyric acid, norepinephrine, and epinephrine, using gold and silver nanoparticles [211]. Additionally, Wang et al. [212] introduced a hybrid nanoarray composed of graphene-Au nanopyramids for the ultrasensitive detection of dopamine and serotonin using SERS with an enhancement factor of approximately 10^{10} [FIGURE 5**A**]. In this study, the fabricated Au Pyramid-Graphene platform effectively improved the SERS signal by synergizing electromagnetic and chemical enhancement on a single substrate, enabling a detection limit as low as 10^{-9} M.

5.3. Protein and Oligonucleotide Detection in Neural Disorders

Over the past several decades, significant efforts have been made to develop advanced biosensors for detecting neurological disease-related proteins. The novel incorporation of hybrid nanomaterials in biosensing will provide attractive opportunities for more sensitive detection of biomarkers to aid in early diagnosis. Hybrid nanomaterials have unique electrical, thermal, optical, and mechanical capabilities due to their nanoscale size and customizable architectures, which contribute to increased analytical performance [204,213-216]. In this section, advances in novel

biosensing strategies for protein detection in neural applications will be discussed.

Recently, a NIR optical nanosensor capable of specific and sensitive detection of Aβ in live cells and *in vivo* was reported by Antman-Passing and coworkers [217]. In this study, SWCNTs functionalized with Aβ42 were utilized for absorbing endogenous Aβ to the SWCNTs surface, resulting in a distinct optical response. This Aβ-modified CNT-based sensor could selectively detect Aβ through modulation of their emission wavelength. The authors also applied this biosensor to a genetically modified mouse model of AD for Aβ measurement, a distinct optical response was observed with age. Furthermore, Li et al. demonstrated a neuroprotective dual-modal nanoprobe for Aβ deposition imaging *in vivo* based on NIR and MRI [218]. Superparamagnetic iron oxide nanoparticles were used as an effective contrast agent. Iron oxide NPs were subsequently modified with a silica shell and carbazole-based cyanine NIR fluorophores, thereby generating the Fe_3O_4@SiO_2@SLCONHR probe for dual-mode imaging. Strong binding interactions between Aβ species and the cyanine fluorophore have given rise to a large fluorescence enhancement in the NIR region. From their investigation, the combination of fluorescence imaging and MRI *in vivo* demonstrated that this nanoprobe was able to permeate through the BBB.

SERS is a powerful analytical tool used for the sensitive detection of pathogenic proteins in many published papers [219-222]. Among them, Yang and co-authors synthesized Ag nanogap shells (AgNGSs) on silica nanoparticles as a SERS nanoprobe for accurate and multiplexed detection of the amyloid peptides Aβ40 and Aβ42 from a patient's blood sample [221]. Raman dyes were embedded in the nanogaps, controlled at the one-nanometer resolution, and generated large SERS enhancement up to 107x between the plasmonic "hot spots" [FIGURE 5**D**]. Antibodies specific to Aβ40 and Aβ42 were also conjugated on AgNGSs to recognize their targets. Using this SERS-based immunoassay, two important AD-related biomarkers, Aβ40 and Aβ42, can be sensitively and simultaneously quantified in human serum.

In addition, optical biosensors for neurodegenerative disease-related protein detection have been extensively investigated using a variety of nanomaterials, one of which being quantum dots (QDs). The NFTs are responsible for destroying transport systems within cells and causing the death of neuronal cells [223]. Compared with age-matched healthy brains, brains with AD have a 4- to 8-fold higher level of p-tau proteins [224]. In light of this fact, abnormal p-tau and tau protein aggregates have been investigated and targeted as representative markers of AD diagnosis. To detect tau in AD, a sandwich structure of tyrosinase (TYR)-induced tau aptamer-tau-tau antibody (anti-tau) was constructed as a fluorescence immunoassay [225]. In this study, dopamine-functionalized core-shell $CuInS_2$/ZnS QDs were employed as fluorophores, exhibiting high luminescence, low toxicity, and excellent biocompatibility. The DA-modified core-shell nanoparticles exhibited good analytical performance for tau, with a linear detection range from 10 pM to 200 nM. In 2015, Chen and co-workers introduced a nanoplasmonic biosensor microarray device to monitor the inflammatory responses of infants after cardiopulmonary bypass (CPB) surgery [226]. In this work, a localized surface plasmon resonance (LSPR)-based microfluidic optical biosensor was developed for parallel multiplex immunoassay of six cytokines (i.e., IL- 2, IL-4, IL-6, IL-10, TNF-α, and interferon γ) with a linear detection range of 5 pg/mL to 20 pg/mL using 1 μL of serum sample [FIGURE 5**C**]. This device was developed via micropatterning on AuNRs, followed by antibody conjugation to those patterns. In addition, this work utilized antibody-conjugated AuNRs together with dark-field imaging to increase sensitivity. A multifunctional magneto-plasmonic nanorod composed of a central nickel component, which was used as an immunomagnetic active component for exosome isolation, flanked by gold at the two ends, which was used as a plasmonic/metal-enhanced fluorescence component, for sensitive exosomal miRNA detection [FIGURE 5**B**] [227]. From their demonstration, the synthesized multifunctional magneto-plasmonic NR exhibit increased miRNA-124 detection levels during neurogenesis of hiPSC-NSCs. Other examples of inorganic nanomaterials as biosensors are highlighted in TABLE 2.

6. Probing Neuronal Stimulation And Differentiation With Functional Inorganic Nanomaterials

6.1. Theragnostic Advancement of Neural Stimulation and Differentiation

Neuronal regeneration is one of the central treatment strategies for both chronic neurological disorders, where the dysfunction is a result of gradual and progressive degeneration of neural cells, and acute CNS injuries, where a traumatic assault causes neurons and neuroglia cells to undergo apoptosis, ultimately leading to discontinuities within the neural network and a loss of function [237]. Stem cell-based neuronal stimulation and differentiation approaches hold tremendous therapeutic potential for treating such disorders and injuries. Various biochemical, biophysical, and electrochemical approaches have been explored to improve stem cell-based neural tissue engineering. Nevertheless, the main limitation is in precisely controlling the differentiation of stem cells into functional neurons, or neuroglia cells, in a real-time in-situ monitored manner. Recent advances in employing theragnostic nanomaterials, combining neuronal differentiation and regeneration capabilities with nondestructive sensing or imaging in one design, have been proven to be valuable in tracking transplanted cells and assessing the therapeutic benefit [238].

The following sections describe the functions of various designs of inorganic nanomaterials for guided neuronal differentiation via small molecule, nucleic acid, and protein delivery. Furthermore, the use of optogenetics, the introduction of biophysical cues, and electronic stimulations are introduced in addition to the nanomaterials' potential to be used as sensing or imaging modalities such as optical imaging, nuclear imaging, and magnetic resonance imaging. This can be accomplished in addition to the potential of the nanomaterials to be used in such ways [239].

6.2. Nanoparticle-Assisted Strategies

A common approach to guide neural stem cell (NSC) differentiation is using nanoparticles. One interesting strategy explored by our group is the development of artificial nanoparticle-based transcription factors called NanoScript, which are designed to mimic both the structure and function of natural transcription factors. This has been accomplished by conjugating several ligands to an AuNP, including a DNA binding domain (DBD), an activation or suppression domain, and a nuclear localization signal [156]. The DBD is a Py-Im hairpin polyamide that can be designed to target specific promotor regions and dictates what transcription factor we are mimicking, while the activation domain is a peptide that aids in recruiting activators and initiating the transcription process. Utilizing this platform, we could drive the differentiation process of NSCs by constructing a Sox9-specific NanoScript capable of repressing the Sox9 gene [FIGURE 6**A**] [158]. This was done by replacing the previously described activation domain with a repression domain, specifically the corepressor peptide WRPW, that has been demonstrated to prevent the formation of basal transcriptional machinery at the binding site and induces repression of genes by the Groucho family proteins.

Table 2
A summary of inorganic nanomaterials for neural sensing and imaging.

NMs	Size	Surface module	Application	Target	Sensing/ imaging modality	LOD/ resolution	Ref.
BIOSENSING							
AuNCs	12 ± 1.5 nm	GQDs	*In vitro*	DA, EP	Electrochemical detection	5, 10 nM	[210]
AgNPs*, AuNPs	35 nm, 61 nm		Neurological diseases	MT, serotonin, DA, GABA, NE, EP	SERS	100 nM	[211]
$CuInS_2$/ ZnS QDs	5 nm	DA	AD	Tau protein	Fluorescence immunoassay	10 pM	[225]
UCNPs*	57.49 nm	SiO_2	PD	MMP3/ UNCP-AIEgen	Fluorescence resonance energy transfer	120 pM	[163]
SPION*	126.6 ± 12.5 nm	SiO_2, SLCONHR	AD	Aβ	Fluorescence, NIR imaging, MRI		[218]
Au-Ni-Au NRs	267/ 745nm	FAM-MB, antiCD63 antibody	hiPSC-NSCs	Exosomal miRNAs	MEF	1 pM	[227]
CNTs	10–20/ 0.5–200nm	ssDNA		DNA	Electrochemical sensing	0.1 mM	[228]
SWCNTs		$(GT)_6$ ssDNA, PEG-PLs	Mouse microglia SIM-A9	DA	Fluorescence		[229]
SWCNTs		Aβ42	AD	Aβ	NIR fluorescence	100 nM	[217]
MWCNTs	10-30 nm/1-10 μm	-COOH, oligonucleotides		DNA	Electrochemical sensing	1.0×10^{-10} $molL^{-1}$	[230]
MWCNTs		CML DNA	DNA detection	DNA	Electrochemical sensing	1fM	[231]
MWCNTs		Polypyrrole, dsDNA	Drug detection	6 MP	Electrochemical sensing	0.08 $\mu molL^{-1}$	[232]
MWCNTs		Fe_2O_3/SnO_2, dsDNA		Doxorubicin	Electrochemical sensing	0.004 $nmolL^{-1}$	[233]
CNT fiber	5∼20 μm		Neural chronic recording		Electrochemical detection, MRI		[234]
Graphene		Fe_3O_4 NPs, NiO NPs	Brain neurotransmitter monitoring	DA, serotonin, NE, EP	Electrochemical detection	5.6 nM, 7.2 nM, 3.5 nM, 6.6 nM	[208]
Graphene-Au nanoarray		Cy5-labeled DNA	hNSCs	Tuj1, GFAP	SERS	1nM	[187]
Graphene-Au nano-pyramid			Neurological monitoring	DA, serotonin	SERS	10^{-10} M	[212]
Au nanocup array		rGO	hNSCs, PC12	DA	Electrochemical detection	100 nM	[188]
AuNR array	40 nm/ 80 nm	Cytokine antibodies	Serum cytokine monitoring	TNF-α, IFN-γ, IL-2, IL-4, IL-6, IL-10	LSPR	∼10 pg/mL	[226]
BIOIMAGING							
AuNPs	15 nm	Levodopa-quinone	PD	AuNPs	Enhanced CT visualization		[137]
AuNPs	60nm∼120nm	Raman active layer	Noninvasive real time imaging	Raman active dye	SERS		[67]
UCNPs*	∼80 nm	$NaErF_4$@$NaYF_4$@$NaGdF_4$: Yb/Tm	*In vivo*	UCNPs	Upconversion luminescence		[164]
UCNPs*	33 × 68 nm	$NaYbF_4$@ $NaYbF_4$: Tm@$NaYbF_4$@SiO_2	Drug-induced neuropathic disorders	Real-time tracking of NPs	Photo luminescence enhancement		[166]
$Gd_2(WO_4)_3$:Eu	270nm	Ethylene glycol	*In vivo*	X-ray fluorescence imaging	Down-conversion radio luminescence		[168]
MENPs	30 nm	Glycerol mono-oleate	*Ex vivo*, *in vivo* delivery	Mesoscopic calcium imaging	Two photon imaging		[157]
USPIONs		PEG	AD	NP tracking, brain imaging	NIR fluorescence, MRI		[159]
MnO_2	120 nm	Macrophage membrane	Acute ischemic stroke *in vivo*	NP tracking, brain imaging	MRI contrast agent, fluorescence		[162]
AuNRs*	4nm/ 68nm	PEG, D1, Ang2	AD	AuNRs	Micro-CT	51 μm	[58]
SiO_2@CNT@AuNP	4.6 μm	PDDA, PSS	*Ex vivo* brain imaging	CNTs, AuNPs	Enhanced NIR optoacoustic-Raman		[235]
CNTs		Sericin	Ischemic stroke	Scaffold tracking	NIR photoluminescence		[155]
SWCNTs			Acute stroke imaging	SWCNT–IRDye800	NIR-IIa window photoluminescence	depth >2 mm, sub-10-μm	[236]
SWCNTs		Protamine, PEG	Stem cell labeling	hMSCs	Photoacoustic imaging, MRI		[68]
SWCNTs	200–500nm	DSPE-mPEG	Deep-tissue anatomical imaging	CNTs	NIR II fluorescent imaging		[65]
SWCNTs	1-2nm /60-300nm	Cyclic Arg-Gly-Asp, PL-PEG	Nanotherapeutics monitoring		Photoacoustic imaging		[66]
SWCNTs	0.6–2 nm	DNA	3T3, CRL-1658, murine myoblast stem cells	CNTs	Fluorescence, cell labeling		[64]

* Materials may have cytotoxicity concerns.
LOD, limit of detection; FAM, fluorescein amidites; MB, molecular beacon; ssDNA, single-stranded DNA; PL, phospholipids; CML, chronic myeloid leukemia; dsDNA, double-stranded DNA; GFAP, glial fibrillary acidic protein; PDDA, poly(diallyl dimethylammonium chloride); PSS, poly (sodium 4-styrene sulfonate); DSPE-mPEG, 1,2-Distearoyl-sn-Glycero-3-Phosphoethanolamine with conjugated methoxyl poly(ethylene glycol).

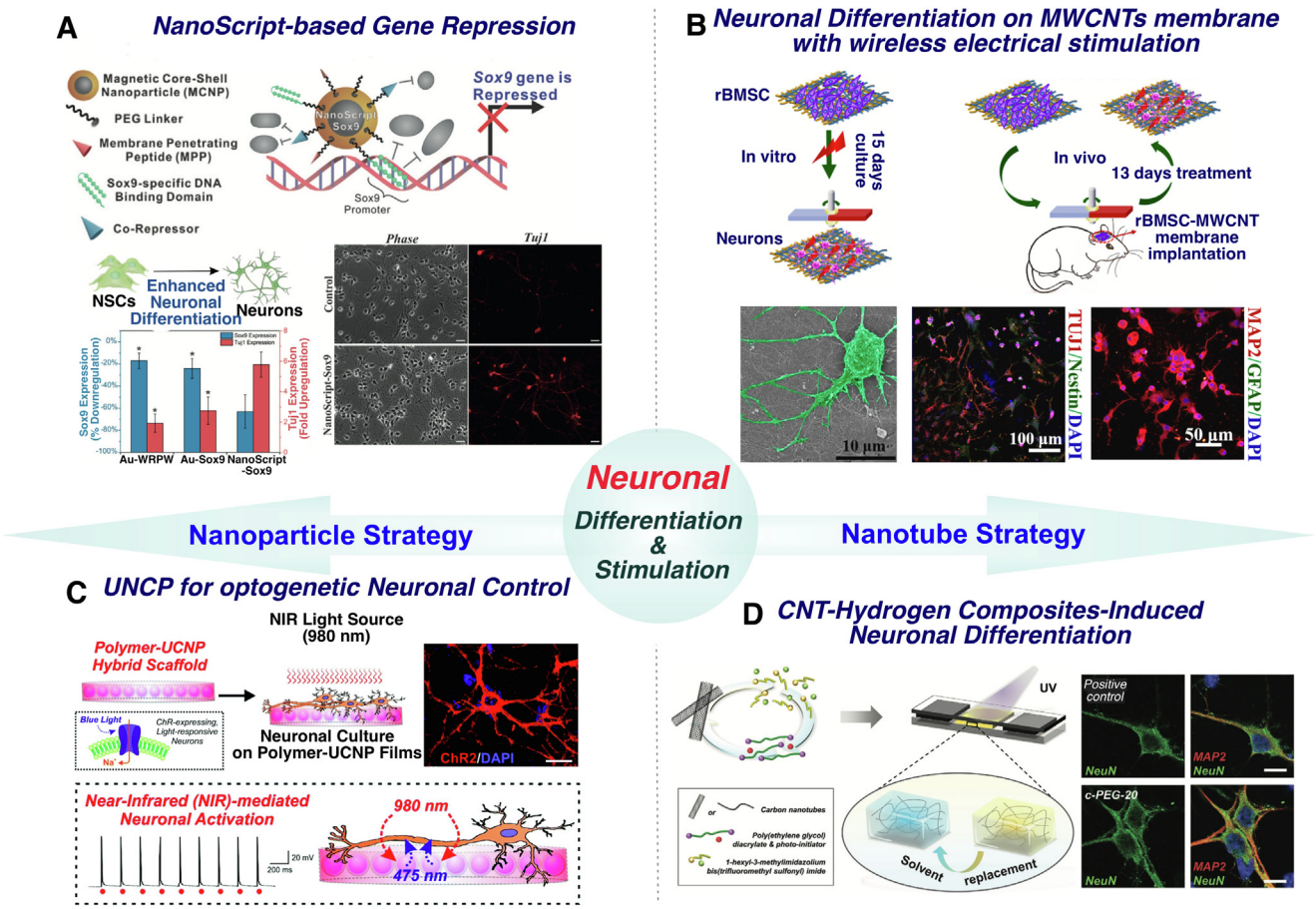

Figure 6. Nanoparticle- and nanotube- assisted strategies for probing neuronal stimulation and differentiation. (A) An artificial transcription factor "NanoScript" for initiating enhanced differentiation of neural stem cell into neurons. (B) Conductive and flexible MWCNT membrane for effectively guiding rat bone-marrow-derived mesenchymal stem cells (rBMSCs) to differentiate into neurons using a wireless localized electrical stimulation system. (C) A hybrid upconversion nanoparticle for optogenetic neuronal control. (D) CNT-hydrogel composites for promoting nerve regeneration. Reproduced with permission [158,173,247,251].

Aside from biomimetic transcription factors, nanoparticles have been utilized as delivery vehicles to introduce small molecules, nucleic acids, and proteins into stem cells in order to drive neuronal differentiation. To this end, mesoporous silica nanoparticles (MSNs) are commonly utilized as they have a large loading capacity and are biocompatible. Chang et al. utilized a MSN to load both a plasmid for Nurr1 and siRNA for Rex1 and co-delivered them into induced pluripotent stem cells (iPSCs) to enhance the differentiation of dopaminergic neurons [161]. Nurr1 is a transcriptional activator that is essential in the development of midbrain dopamine neurons while the knockdown of Rex1 increases the expression of late neuronal markers, such as MAP2 and Nestin, while synergistically enhancing dopamine expression in neural cells [240-242]. Through a combination of immunostaining, flow cytometry, and ELISA, the authors demonstrated an increase in Tuj1, MAP2, Nestin, dopamine transporter, and dopamine expression 7- and 14-days post-treatment of the iPSCs in their co-delivered system relative to the nontreated control and the delivered plasmid. Similarly, the same group co-delivered three plasmids adsorbed onto the surface of different MSNs in addition to the small molecule drug ISX-9, attached via avidin-biotin interactions, to transdifferentiate fibroblasts into functional dopaminergic neurons [160]. The plasmids utilized included Ascl1, Brn2, and Myt1l, as these have been reported in the literature to directly convert fibroblasts to neurons [243]. By utilizing this nonviral delivery method, the authors reported that by 19 days there was a significant expression of dopamine transporter in addition to a significant increase in the concentration of dopamine present by day 22 compared to the controls and the cells treated without the ISX-9 drug.

Recently, there have been studies that aim to spatially and temporally control stem cell differentiation into neurons by utilizing nanoparticles that can be controlled by external forces in lieu of chemical factors within the cells. One of the key driving forces for this is that the adult mammalian brain can still undergo neurogenesis, whereby new neurons develop and mature before functioning into existing neural circuitry. This process has been reviewed elsewhere and has been shown to affect cognition and mood, when observing the hippocampus, and has cognitive and behavioral implications (i.e., pattern separation as well as anxiety and depressive-like behavior respectively) [244]. With this framework in mind, there has been a great amount of work focusing on UCNP-based nanoparticle platforms and their ability to selectively regulate cells irradiated with NIR in a spatiotemporal manner. Zhang et al. demonstrated that human iPSC-derived neural stem cells (hiPSC-NSCs) were delivered retinoic acid in a remote-controlled manner to control their differentiation into neurons [159]. The core of the system is a core-shell-shell UCNP composed of $NaYF_4$:Yb/Tm@ $NaYF_4$:Yb/Nd@$NaYF_4$ prior to being coated with a mesoporous silica coating and functionalized with the photoswitching dye spiropyran. For this system, Nd was chosen as it allows the system to be excited at 808 nm instead of 980 nm, thereby affording deeper tissue penetration and less heating effects compared to the 980 nm excitation that is more readily absorbed by water. Moreover, the full composition is designed to block

energy cross-relaxation while maximizing emissions between 250 nm and 380 nm, the range of light required to switch spiropyran to the open merocyanine form. In this way, soluble cues, such as retinoic acid, could be loaded into the mesoporous silica and would not release until excited by the emissions of the UCNP. Upon treatment of hiPSC-NSCs with this platform, it was shown that the system, when irritated with 808 nm light, had significant neurite outgrowth, increased Tuj1, MAP2, and synapsin expression, and were functional neurons via calcium imaging.

Upconversion nanoparticles have gained growing research interest in nanobiosensing due to their high photostability, low auto-fluorescent background, and deep tissue penetration. However, the application of UCNPs is limited by their low emission intensity. To address the aforementioned issue, a single-crystal core–shell-shell "sandwich" structured UCNP was synthesized to minimize the energy back-transfer to yield bright visible emissions. These UCNPs exhibited a remarkable enhancement of luminescent output. Because of its enhanced emission, this designed core-shell–shell UCNP was subsequently applied to develop a highly sensitive biosensor for the detection of dopamine released from stem cell-derived dopaminergic neurons and monitoring neurological differentiation at a single-cell scale.

Another well-known area UCNPs are utilized in optogenetics, where the activity and functions of specific cell types can be controlled and studied with high spatiotemporal resolution and reduce damage to living organisms compared to UV-based platforms. In this way, researchers can leverage the use of opsin-expressing neurons via controlled activation or inhibition of specific cellular signaling pathways. In the former scenario, neural pathways can either be activated or suppressed via the remote activation of UCNPs. Traditionally, the activation of these pathways has been more successfully achieved as suppression requires a larger magnitude of optical power that is red-shifted to appropriately inhibit the required opsin proteins [165]. Specifically, this is because the stimulators channelrhodopsin-2 (ChR2) and VChR1 excite around 475 nm and 545 nm, respectively, which corresponds well with $NaYF_4$:Yb/Tm and $NaYF_4$:Yb/Er UCNPs. While on the other hand, the inhibitors halorhodopsin (NpHR) and archaerhodopsin (ArCH) have maximum excitations at 590 nm and 566 nm, respectively, which UCNPs do not have an effective emissions peak in this region [245]. One example of UCNP activation of neural pathways was demonstrated utilizing a Yb^{3+}-Tm^{3+} doped UCNP to generate a blue emission compatible with the ChR2, a protein that undergoes conformational changes following activation, allowing positively charged ions to depolarize cells [131,246]. In this study, tyrosine hydroxylase-driven Cre recombinase transgenic mice were injected with an adeno-associated virus for ChR2-EYFP to allow for Cre-dependent expression of ChR2 in dopaminergic neurons in the ventral tegmental area of the brain. It was found that following 980 nm excitation a significantly larger number of neurons were firing action potentials, which was validated by observing the expression of *c-fos,* relative to their controls. Similar studies were conducted by Dr. Han's group in 2016 and Dr. Lee's group in 2015. Dr. Han's lab utilized a core-shell UCNP consisting of Yb^{3+}-Er^{3+} that was sensitive to an IR-806 dye to activate a red-shifted variant of channelrhodopsin (ReaChR), while our group utilized a Yb^{3+}-Tm^{3+} UCNP embedded in a polymeric film to activate neurons [FIGURE 6**C**] [247]. In 2018, a core-shell-shell ($NaYF_4$@ $NaYF_4$Yb/Er@ $NaYF_4$) UCNP was developed that utilized 78 mol% Yb and 2 mol% Er to maximize a 2-photon process that was theorized to produce 540-570 nm emission to match the opsin protein light-gated Cl^- ion pump enhanced NpHR [165]. It was highlighted that by introducing these particles into the motor cortex of mice, they could modulate these animals' locomotion in an open field.

6.3. Nanotube-Assisted Strategies

Carbon nanotubes have been widely used for designing biosensing systems to detect proteins [248], nucleic acids [228,230,231], reactive oxygen species [249], therapeutic drugs [233], and small molecules [250]. Kirschner et al. reported using CNTs to modify the surface of a biosensor and leveraged the native surface plasmon resonance of CNTs for real-time protein binding measurements [248]. The following year, Cai and co-workers fabricated carboxylic acid functionalized MWCNTs as an electrochemical biosensor for covalent DNA immobilization and enhanced hybridization detection [230]. More recently, Shahrokhian et al. developed an ultrasensitive detection method for specific DNA sequences based on MWCNTs and a hairpin oligonucleotide switch. In this design, changes to the surface conductivity, based on the MWCNT replacement, were monitored by using an electrochemical redox pair, and the linear correlation range of the model target DNA was reported to be from 10 pM - 0.1 μM [228]. Later, Ghrera et al. fabricated a microfluidic chip with MWCNTs being electrophoretically deposited onto patterned indium tin oxide (ITO) coated glass substrates for electrochemical sensing. In this design, complementary target DNA was monitored with an excellent calibration range from 1fM to 1 μM and a response time of 60 s [231]. Additionally, Karimi-Maleh et al. incorporated functionalized-MWCNTs on a graphite electrode modified with polypyrrole and equipped with immobilized DNA to detect 6-mercaptopurine, a therapeutic small molecule drug [232]. These advanced designs of ultrasensitive CNT-based biosensors paved the way for broader cellular applications, specifically characterizing cellular behavior and monitoring cell fate.

Furthermore, CNTs are instrumental in regenerating and repairing irreversibly diseased or damaged nerve tissues in the peripheral and central nervous system. Most recently, a wirelessly trigged local electrical stimulation system was established to specifically induce neuronal differentiation from rat bone-marrow-derived mesenchymal stem cells (rBMSCs) by coupling a highly conductive and flexible multi-wall carbon nanotube membrane with a rotating magnetic field by Liang and collaborators [FIGURE 6**B**] [251]. They innovatively developed this method for the transdifferentiation of MSCs into neurons as an alternative to using neural stem cells to treat neurodegenerative diseases. In this work, a conductive and flexible MWCNT membrane was prepared and seeded with rBMSCs. Following the introduction of a wireless localized electrical stimulation system, the fabricated MWCNT membrane could effectively guide rBMSCs to differentiate into neurons without biological or chemical differentiation factors. Hu et al. reported the use of chemically modified CNTs to promote neuronal growth. By varying the functional groups present on the functionalized-CNTs, the authors were able to determine that surface charge contributes to neurite outgrowth and branching. Additionally, the positively charged and zwitterionic MWCNTs were found to have the beneficial attribute of increasing the length and branching of neurites [180]. Malarkey et al. investigated how the SWCNT−PEG substrates can affect cellular and protein adherence, influence protein expression, promote neuronal growth, and induce neurite outgrowth by controlling their conductivity [176]. The superiority of CNTs in neuronal stimulation and differentiation also reflects their flexibility in incorporating them with other materials. For instance, Ye and coworkers developed CNT-hydrogel composites to facilitate neuronal differentiation [FIGURE 6**D**] [173]. In this work, the CNT-embedded composites could affect neurogenesis and maintain homeostasis of network activity. Thus, CNT-based scaffolds have shown to be advantageous for use as neuronal implants *in vivo* to support neuronal growth with excellent mechanical strength and flexibility [252].

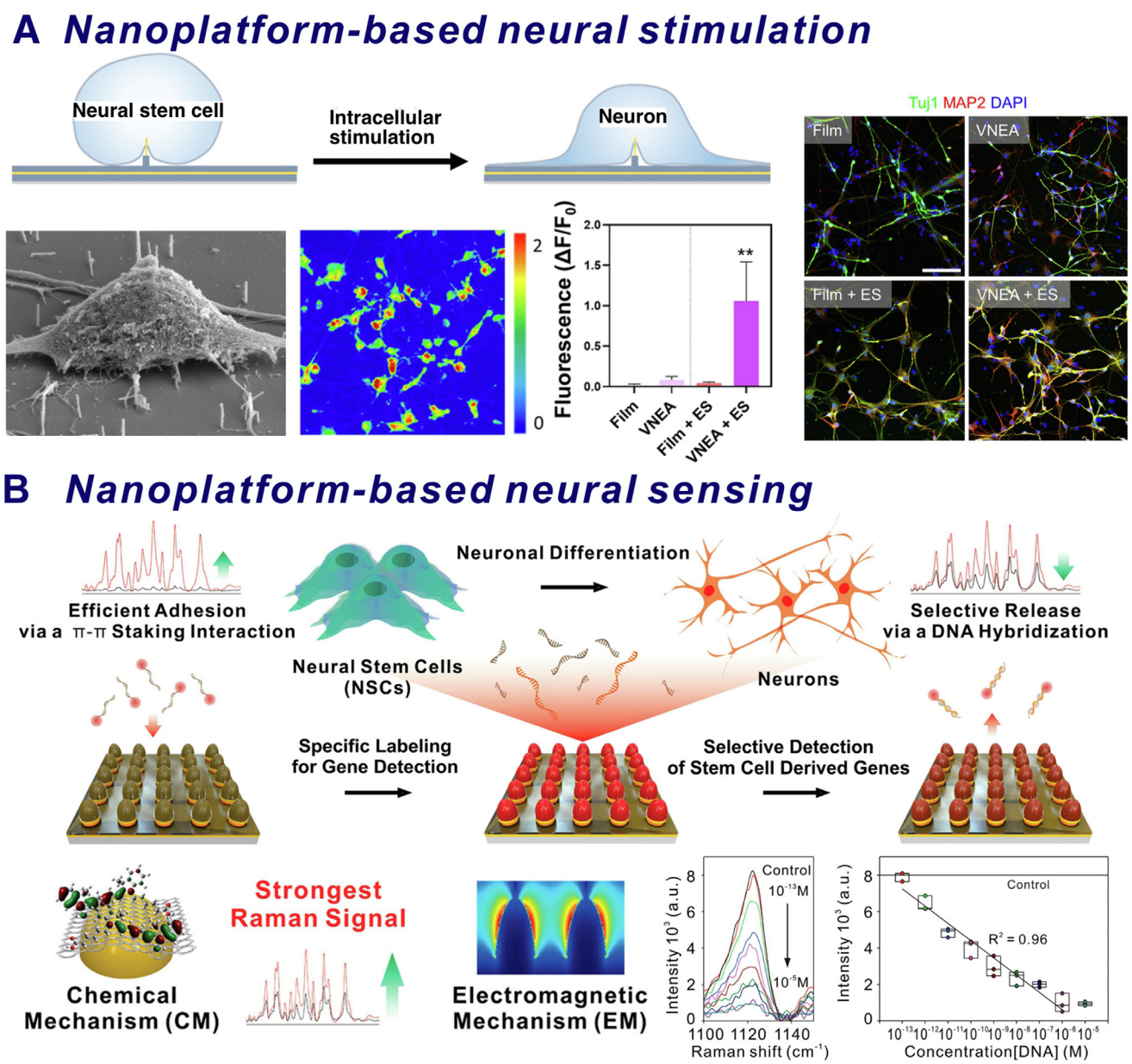

Figure 7. Nanoplatform based neural stimulation and sensing. Nanoplatform-based strategies for stimulating neuronal differentiating and in-situ monitoring. (A) A vertical nanowire electrode array (VNEA) to penetrate and directly provide electrical potential and current to cells via nanoelectrodes for effective intracellular stimulation to promote hfNSC neurogenesis. Immunofluorescence imaging, qPCR, and Ca^{2+} imaging of FAM-treated hfNSCs showed the technical advantages of VNEA-mediated direct intracellular electrical stimulation over extracellular electrical stimulation by demonstrating improved neuronal differentiation, maturation, and functionality of hfNSCs. (B) A graphene-coated homogeneous plasmonic gold hybrid nanoarray for a dual-enhanced (electromagnetic and chemical mechanism) SERS-based quantification of Tuj1 gene expression levels to characterize neuronal differentiation of hNSCs. Using a dye-labeled complimentary oligonucleotide probe, the dynamic range of detection was reported to range from 100 fM - 10 μM. Reproduced with permission [183,187].

6.4. Theragnostic Nanoplatforms

Stem cell therapy is one of the emerging fields in neuron regenerative medicine. Neurological disorders, such as AD, PD, and HD, are associated with profound loss of functional neurons. Transplantation of neural stem cells to damaged regions will help the functional recovery through stem cell differentiation into neurons. Therefore, close monitoring of the neurogenic differentiation is extremely important for effectively controlling stem cell fate and evaluating the response of treatments. Nanomaterials that incorporate biosensors have attracted much research interest in this field. Lee et al. developed a label-free capacitance sensor array to monitor the differentiation of human fetal brain-derived NSCs (hfNSCs) in a real-time manner, as well as identify the fates of differentiated cells [253]. The hfNSCs were inserted between two gold electrodes, and capacitance changes were measured to determine cellular activity. A slow increase in capacitance with peak formation was observed when hfNSCs were cultured in differentiation conditions. In contrast, a steady and rapid increase in capacitance without peak formation was obtained in proliferation culture conditions, indicating that the proliferation and differentiation status of hfNSCs can be distinguished in real-time.

Nanoarray substrates contribute to the increased sensing performance of nanoplatforms due to their periodic nanoscale patterns. A large-scale homogeneous nanocup electrode array (LHONA) for the detection of dopamine release from dopaminergic

cell lines, as well as the monitoring of differentiation of hNSCs into dopaminergic neurons, was introduced by Kim and coworkers [188]. The resulting LHONA platform could achieve real-time and highly sensitive electrochemical detection of neurotransmitters that are produced by dopaminergic cells. From the distinguished differences in DA production, the LHONA sensor could discriminate dopaminergic neurons from other types of cells to monitor neural stem cell differentiation. The LHONA platform was composed of distinct periodic cup-like nanostructures generated on an ITO electrode using laser interference lithography (LIL) and electrochemical deposition methods. From their demonstration, LHONA could serve as an excellent platform for the sensitive detection of both DA from a model dopaminergic cell line (PC12) and dopaminergic neurons derived from hNSCs via the direct attachment/culturing of cells on the surface of the nanoarrays. A similar study by Know et al. utilized a vertical nanowire electrode array (VNEA) to provide electrical potential and current to hfNSCs. By activating these cells with intracellular electrical stimulation, it was found that VNEA is capable of improving neuronal differentiation and facilitating functional maturation of hfNSCs due to enhanced voltage-dependent ion-channel activity [FIGURE 7**A**] [183].

Aside from electromagnetic and chemical-based sensing methods, our group has utilized SERS in various platforms to detect specific differentiation markers. Yang et al. designed a dual-enhanced SERS sensing platform, using graphene-coated homogeneous plasmonic metal (Au) nanoarrays as the substrate, to detect and quantify Tuj1 gene expression level and characterize neuronal differentiation of hNSCs [FIGURE 7**B**] [187]. The homogeneous graphene-plasmonic hybrid nanoplatform generated by LIL exhibited great potential to be extended to various sensing applications. In another study, exosomal miRNA was used as a stable biomarker for monitoring neurogenesis.

7. Nanomaterial-Guided Differentiation Of Supporting Cells For Neuronal Therapy

7.1. Supporting Cells in Neural Disorders

While neurons are widely regarded as the functional core of the CNS, glial cells also play an important role in structural maintenance and neurological function. Especially in the CNS, glial cells are the most abundant cell type, serving in almost every aspect of neural activity, and are critical in modulating communication between nerve cells [254]. Glial cells of the CNS include oligodendrocytes (ODCs), astrocytes, microglia, and ependymal cells. Oligodendrocytes provide support and insulation to neurons by forming the myelin sheath around axons. Astrocytes are essential for connecting neurons and capillaries to exchange nutrients and substances, maintain the extracellular environment, and provide structural support. More importantly, astrocytes are also the main component of the BBB, which, as previously described, is the most pivotal structure in the CNS that prohibits the entrance of toxic substances into the brain. Microglia constantly scavenge pathogens and dead cells and act as the main form of active immune defense in the CNS in response to infections or tissue damage. Ependymal cells are mainly involved in cerebrospinal fluid production as a choroid plexus component [255].

The function of glial cells has been extensively studied to reveal the role these cells play in both the function and dysfunctions of the CNS [FIGURE 8**A**]. Recent advances demonstrate that glial cells are implicated in the progression of neurodegeneration, either through the loss of normal function or the introduction of abnormal function. Additional evidence suggested that genetic alterations and dysfunctions are involved in the pathophysiology of several neurodegenerative diseases, including PD, AD, Amyotrophic lateral sclerosis (ALS), epilepsy, and frontotemporal dementia. Several studies have also shown that systemic inflammation and infections induce a transitory state in microglia, leading to changes in their state and function. Moreover, subsequent microglial priming may be involved in developing neurodegenerative diseases, including PD, AD, and ALS [256,257]. Similarly, the activation of microglia was found to promote astrocyte activation. As part of this process, the genes and proteins associated with astrocytes, as well as the morphological structure and physiological function of astrocytes, go through a series of progressive changes. The loss of intended function, or an increase in the toxic function, of astrocytes, can cause nerve excitotoxicity, oxidative stress, and inflammatory response in neurodegenerative disease development [258].

One of the current neurodegeneration treatment strategies is targeting nicotinamide adenine dinucleotide (NAD), which regulates inflammatory repair processes in glial cells. Roboon et al. demonstrated that CD38, the enzyme that hydrolyzes NAD and controls its bioavailability, was upregulated in microglia after cuprizone-induced demyelination in a mouse model. The reduced clearance of degraded myelin and ODC repopulation, suppressed glial activation, and enhanced neuroinflammation were all associated with the knockout of CD38 [259]. Petković et al. went through a different pathway of using transgenic-produced astrocyte-targeted IL-6 (GFAP-IL6Tg) in a cuprizone-induced demyelination model of multiple sclerosis to elicit a reduction in microglial accumulation and activation, removal of degraded myelin, and reduced axonal protection [260]. The suppression of the CSF1R pathway is another strategy for decreasing microglial proliferation and accumulation. Martínez-Muriana et al. administrated GW2580, a selective CSF1R inhibitor, to reduce microglial proliferation in an ALS mouse model and demonstrated the ability to slow disease progression, attenuate neuronal death, and extend animal survival. Their findings proved that CSF1R signaling regulates inflammation in the CNS of ALS mice, highlighting the therapeutic potential of CSF1R for ALS treatment [261].

7.2. Nanomaterial-guided Oligodendrocyte Differentiation

Oligodendrocytes are glial cells that play important roles in maintaining the function of the CNS, including forming myelin sheaths and providing support and insulation to axons for neuronal signaling [262,263]. Loss of ODCs may cause demyelination and further induce neurodegenerative diseases [264]. Stem cell therapy, a treatment strategy that replaces damaged ODCs with cells differentiated from human iPSC, is an emerging way to repair myelin-related function loss. However, only limited clinical trials of stem cell therapies have been proven to generate stem cell-derived ODCs. Recent progress in nanotechnology has inspired the development of nanomaterial-assisted cellular proliferation and differentiation for neural applications [265,266]. The synthetic effect of nanomaterials and stem cell engineering will suggest more possibilities to address current challenges in stem cell therapies. From a therapeutic perspective, selective and proper differentiation of neurons and ODCs from neural stem cells is vital to successfully recover CNS function. In recent years, many research papers have been reported to investigate the promising potential of using nanoscale materials to control ODC differentiation. Stem cell differentiation can be controlled by changing topographical, biochemical, and electrical cues [267,268]. This section will discuss the recent progress of nanomaterial-guided ODC differentiation.

Nanofibers have emerged as interesting nanostructures in regenerative medicine [269]. Diameter, density, conductivity, surface modification, and other properties of nanofibrous structures can be tuned to create optimal nano scaffolds for enhanced ODC differentiation. The superiority of nanofibers in guiding stem cell

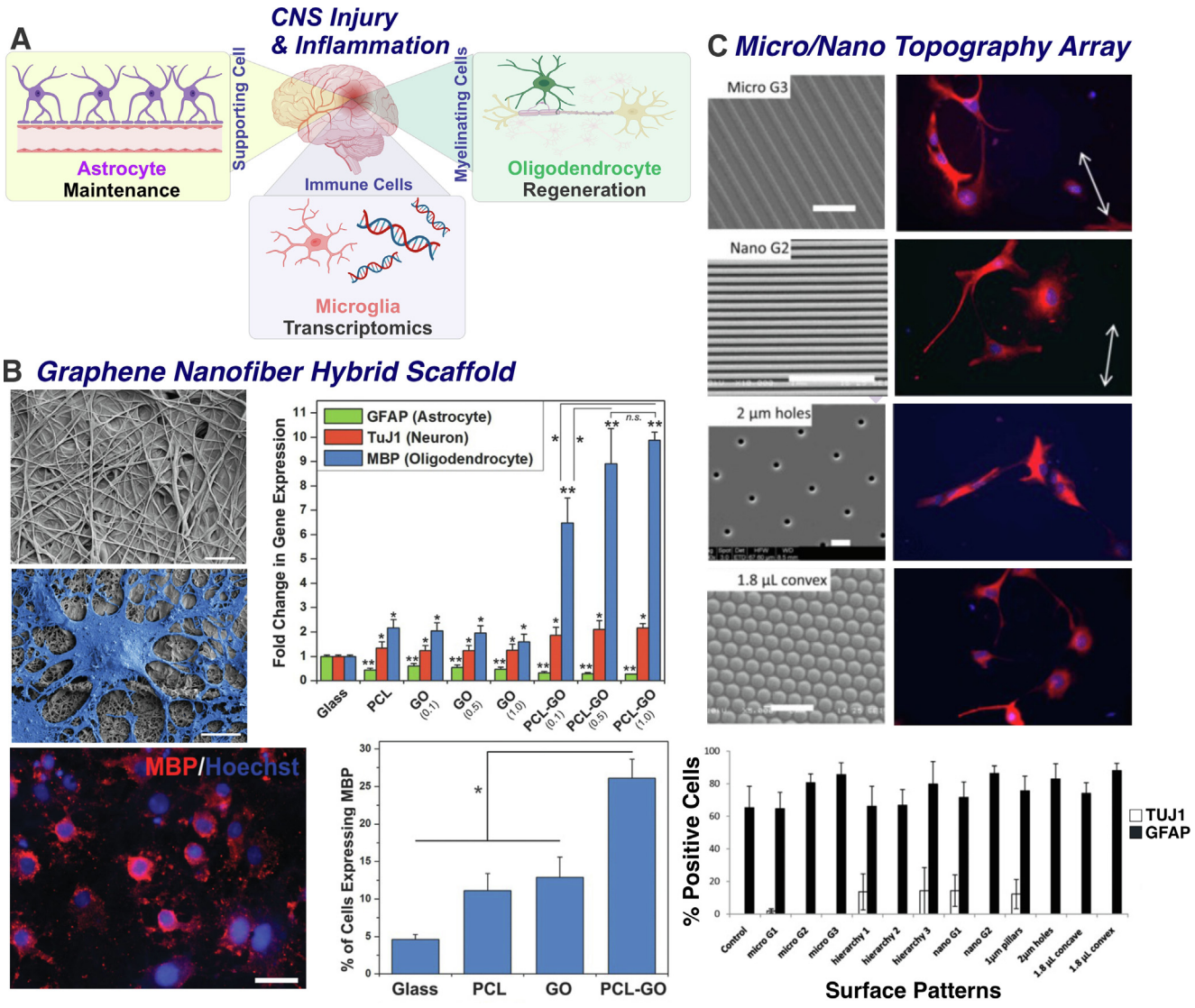

Figure 8. Differentiation of NSCs into supporting cells of the CNS. (A) The role of supporting cells in the CNS. (B) FE-SEM images of graphene-PCL nanofiber hybrid scaffold with seeded neural stem cells. Immunostaining following 6-days of culture show both early and mature oligodendrocyte markers Oligo2 and MBP respectively. PCR highlighting ODC differentiation on various substrates. (C) Various nano- and micropatterns used to optimize astrocyte differentiation. GFAP and TUJ1 expression highlight which pattern characteristics favor astrocyte verse neuronal differentiation. Reproduced with permission [182,189].

fate lies in their large surface area, porosity, and ease and flexibility of surface functionalization. More importantly, the nanofibrous network mimicking the extracellular matrix provides a favorable environment for cell proliferation and differentiation. Electrospinning is an effective strategy to generate nanofibrous structures using polymers, such as poly(caprolactone) (PCL), poly(L-Lactic acid) (PLLA), and PLLA/collagen blend. PCL is the most applied material among them because of its biocompatibility and biodegradability. Shah et al. developed a hybrid nano scaffold composed of GO-coated PCL nanofibers to guide NSCs differentiation into ODCs [FIGURE 8**B**] [182]. Graphene oxide, a graphene-based nanomaterial with a sheet structure, has been shown to have advantages in NSC culture due to its unique chemical, electrical and mechanical properties. In this work, the authors found that the nanofiber-GO hybrid structure outperformed the individual components in a synergistic manner with enhanced and selective ODC differentiation. Thus, this demonstrated how the nanofiber's morphology and GO's electronic properties could promote differentiation. The enhanced and selective ODC differentiation was also confirmed with a significant increase of MBP gene expression, which is a key marker of ODCs, and a simultaneous decrease in expression of an astrocytic glial fibrillary acidic protein, and a slight upregulation of the gene Tuj1. Overall, this study demonstrates that physical cues of cell culture conditions will lead to the selective differentiation of NSC into mature ODCs without adding growth factors, further highlighting the promising role of nanomaterials in neural regeneration applications.

Recently, AuNRs have also been reported to promote stem cell differentiation. Sharma and the authors introduced a gold nanorod substrate to promote the differentiation of rat fetal NSCs into ODCs [169]. Gold nanomaterials distinguish themselves with biocompatibility and electrical conductivity, which may provide a conducive surface for stem cell differentiation. In this study, the functionalized substrate was fabricated using a layer-by-layer approach, and AuNRs were synthesized and coated on the substrate's surface, followed by seeding ODC progenitor cells for differentiation. As a result, enhanced ODC differentiation was observed on the functionalized AuNR substrate compared with conventional poly-D-lysine (PDL)-coated substrate.

7.3. Nanomaterial-guided Astrocyte Differentiation

Astrocytes play various critical roles in maintaining the neurophysiological function of the CNS by secreting trophic molecules, modulating the brain's microenvironment, maintaining BBB integrity, and increasing synaptic plasticity. Astrocytes are activated in response to neuroinflammation during the progression of pathological changes, which are found to be associated with neurodegenerative disorders [270]. Recently, fundamental studies, including astrocyte pathological and functional studies in addition to astrocyte differentiation, offered great potential for applications in both *in vitro* BBB modeling and astrocyte-targeting novel approaches for neurodegenerative disease treatment. Nanomaterials are a powerful tool for delivering therapeutics and providing biophysical signals that have been wildly utilized for guided astrocyte differentiation.

Szarowski et al. found that astrocytes prefer to adhere and proliferate on patterned surfaces of varying dimensions compared to smooth silicon surfaces *in vitro* [271]. Moe et al. further studied topological regulations of neuronal differentiation and astrocytic differentiation using a customizable multi-architectural chip array with isotropic and anisotropic features, ranging from nano- to micrometer dimensions, in addition to various aspect ratios and hierarchical structures [FIGURE 8**C**]. Experimental results demonstrate that the highest percentage of GFAP-positive astrocytes differentiated from murine NPCs was observed on the architectures of 2 μm holes, 1 μm pillars, and 1.8 μm microlenses for an average percent differentiation of 85% and above. Meanwhile, the other non-astrocyte-promoting structures or neuron-favored structures gave much lower factions of differentiated astrocytes, approximately 50∼60% [189]. This systematic study provided a solid foundation for regulating astrocyte differentiation by modulating biophysical signals through a nanomaterial-guided approach. Similarly, Pandanaboina et al., integrated plasmonic gold nanorods into a 2D architecture to stimulate, modulate NSCs, and tune cell physiology. Moreover, the result, characterized by determining GFAP-positive cells, showed a significant increase in astrocytic differentiation from 19.77% on the traditional PDL-laminin flat surface to 36.46% on the AuNR surface, a nearly doubled number of differentiated cells on day 10 in the AuNR group, and a larger astrocyte population on AuNRs relative to the PDL-laminin, 43.37%, and 39.85% respectively. In conclusion, the functionalized AuNRs in this study were shown to be non-toxic to NSCs, accelerate differentiation, and promote astrocyte generation [190]. Combining the nanostructured interfaces and the functional inorganic nanomaterials with rich charge density, Posati et al. employed hydrotalcite-like compounds (HTlc), which has a formula of $[Zn_{0.72}Al_{0.28}(OH)_2]Br_{0.28}0.69H_2O$, to form thin-films with rod-like structures from simple aqueous colloidal dispersion to evaluate the cellular and functional behavior of rat neocortical astrocytes interacting with the HTlc. They show that HTlc films are biocompatible and do not promote the gliotic reaction while favoring astrocyte differentiation by induction of F-actin fiber alignment and vinculin polarization. In conclusion, their use of nanoscale HTlc could promote astrocytes growth and differentiation, mimic the interaction of astrocytes with the ECM, and open a new route for generating *in vitro* BBB models while also benefiting pathological studies for neurodegenerative disorders [191].

Blumenthal et al. discovered that nanoroughness also influences neuron-astrocyte interaction via mechanosensing cation channels. They simulated random ECM nanoroughness using an assembly of monodispersed silica colloids of increasing size from 3.5 nm to 80 nm. The results demonstrated that nanoroughness changes affect differentiated neuron-to-astrocyte ratio and alter the apical roughness of healthy astrocytes, thus affecting neuron-astrocyte attachment and neuronal survival. The authors further analyzed the topographical characteristics of Aβ plaques in the human brain and found an increased tissue nanoroughness in regions of amyloid plaque buildup in AD patients' brains. Their key findings linked astrocytes and ECM-induced topographical changes in neuronal pathologies and provided new insights for developing therapeutic targets for AD treatment [192].

One of the astrocytes' critical functions is to display bioelectrical activity mediated by ion channel proteins. However, *in vitro* cultured astrocytes normally do not closely resemble the bioelectrical properties as they do *in vivo*, thus making it challenging for the noninvasive electrophysiological recording of astrocytes. Saracino et al. designed a recording site based on randomly oriented gold coated-silicon nanowires (NWs). Fluorescein diacetate staining, Alamar Blue assay, and an actin cytoskeleton study with phalloidin F-actin staining analyses demonstrated that Au/SiNWs promoted cellular adhesion, growth, and differentiation of astrocytes with star-like morphology. On the other hand, the nanostructured electrodes with remarkable signal detecting abilities, due to the large effective surface area, the tight junction NW/astrocyte-endfeet, and a possible NW engulfment into the cell membrane, were able to identify the spectral range of differentiated astrocytes transmembrane voltage oscillations and their power. By utilizing the Au/SiNWs nanoarray, this study performed enhanced astrocyte proliferation and differentiation, allowed for in situ recording of slow oscillations from differentiated astrocytes, and presented a reliable approach to study the role of astrocytic function in brain physiology and pathologies [170]. Another major application of nanomaterial-guided astrocytic differentiation is for dynamic BBB development. Very recently, Mantecón-Oria et al. combined various graphene-based nanomaterials (GBNs) with PCL and tested their influence on astrocytic differentiation. The physicochemical, electrical, and topographical properties, protein adsorption capacity, and biological functionality of the PCL/GBN scaffolds were evaluated. The differentiated astrocytic morphology change revealed that reduced-GO and GO membranes were the most favorable GBNs for the enhancement of astrocytic differentiation. Overall, this study pointed out GBNs key features for future research on 3D PCL/graphene composite hollow fiber membranes for *in vitro* neural and BBB models [193].

8. Summary And Future Perspectives

Theragnostic nanomaterials, regardless of their dimensionality, provide a powerful and versatile way for scientists to modulate, monitor, and understand cells and cellular processes in the CNS. One of the biggest advantages of these materials is that they can be utilized for early diagnosis in a nondestructive manner while delivering a therapeutic agent of interest in a targeted manner. Moreover, some materials, such as AuNCs, can passively enter the CNS and later be excreted via urination. Meanwhile other platforms, such as UCNP-based dopamine sensors, can detect their biomarkers in a sensitive and selective manner with a picomolar detection limit. Such a feat is difficult with traditional approaches, which may be more destructive or when a diagnosis is only made after a patient begins displaying symptoms. Moreover, targeting specific cells, such as microglia, can have implications in many neurological disorders, where neuroinflammation is a common occurrence, as well as in TBI and SCI. Similarly, nanomaterials have the advantage of being easily tunable, implying that the target cells or the detected biomarker can readily be changed for a specific disease of interest. For 0D materials, this can include PEGylating the surface to increase colloidal stability, conjugating various antibodies or targeting ligands for improved targetability, and nuclear localization to influence the transcriptomic profile of cells, thereby altering their fate. This may include surface functionality for 1D

and 2D materials but also designing composite materials with unique degradation profiles and monitoring systems *in vivo*. The latter is crucial when delivering cells as a therapeutic option into the CNS on an inorganic scaffold; being able to monitor the degradation of the materials and possibly cell differentiation and integration can provide valuable insight for scientists.

Scientists can improve their systems to regulate biological processes or monitor biomarkers of interest *in vivo* or *ex vivo* by properly designing a material through dimensionality, hydrophilicity, size, charge, or material composition. For example, MNPs can be used as MR contrast agents while also guiding the particle to the desired location. Similarly, UCNPs serve as light transducers and can allow deep tissue activation following excitation with NIR light to activate or suppress biological processes or spatiotemporally release a therapeutic agent of interest while also conferring imaging capabilities. In other cases, the material themselves, and not what is either loaded or adsorbed to them, can elicit an enhanced response or strengthen a detectable signal, as is observed with CNTs and AuNCs. Thus, selecting the optimal nanomaterial with proper dimensionality requires careful consideration to achieve maximum theragnostic efficiency. Understanding the physiochemical properties of these materials, what they can offer, and how they can interface with the CNS and the patient's body as a whole will allow researchers to address challenges in theragnostic applications or afford them the ability to further probe biological processes that drive the design of future materials and applications. Ultimately, tuning the dimensionality of a nanomaterial and the material composition itself can effectively counteract disease progression and allow for early diagnosis that benefits the patient, thus improving their quality of life.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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