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Nanotechnology for Neuroscience: Promising Approaches for Diagnostics, Therapeutics and Brain Activity Mapping

Anil Kumar,
State Key Laboratory of Crystal Materials, Shandong University, Jinan 250100, China

Department of Chemistry, Bio-Imaging Research Center, University of Georgia, Athens, Georgia 30602, United States

Beijing Institute of Nanoenergy and Nanosystems,Chinese Academy of Sciences,Beijing, China

Aaron Tan,
UCL Medical School, University College London (UCL), London, United Kingdom

Biomaterials and Advanced Drug Delivery Laboratory (BioADD), Stanford University School of Medicine, Stanford University, Palo Alto, California, United States

Joanna Wong,
Imperial College School of Medicine, Imperial College London,London, United Kingdom

Jonathan Clayton Spagnoli,
Department of Chemistry, Bio-Imaging Research Center, University of Georgia, Athens, Georgia 30602, United States

James Lam,
UCL Medical School, University College London (UCL), London, United Kingdom

Queens' College, University of Cambridge, Cambridge, United Kingdom

Brianna Diane Blevins,
Department of Chemistry, Bio-Imaging Research Center, University of Georgia, Athens, Georgia 30602, United States

Natasha G,
UCL Medical School, University College London (UCL), London, United Kingdom

Lewis Thorne,
Department of Neurosurgery, National Hospital for Neurology and Neurosurgery, Queen Square, London, United Kingdom

Keyoumars Ashkan,
Department of Neurosurgery, King's College Hospital NHS Foundation Trust, King's College London, London, United Kingdom

Jin Xie, and

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Department of Chemistry, Bio-Imaging Research Center, University of Georgia, Athens, Georgia 30602, United States

Hong Liu

State Key Laboratory of Crystal Materials, Shandong University, Jinan 250100, China

Beijing Institute of Nanoenergy and Nanosystems,Chinese Academy of Sciences,Beijing, China

Abstract

Unlocking the secrets of the brain is a task fraught with complexity and challenge – not least due to the intricacy of the circuits involved. With advancements in the scale and precision of scientific technologies, we are increasingly equipped to explore how these components interact to produce a vast range of outputs that constitute function and disease. Here, an insight is offered into key areas in which the marriage of neuroscience and nanotechnology has revolutionized the industry. The evolution of ever more sophisticated nanomaterials culminates in network-operant functionalized agents. In turn, these materials contribute to novel diagnostic and therapeutic strategies, including drug delivery, neuroprotection, neural regeneration, neuroimaging and neurosurgery. Further, the entrance of nanotechnology into future research arenas including optogenetics, molecular/ion sensing and monitoring, and piezoelectric effects is discussed. Finally, considerations in nanoneurotoxicity, the main barrier to clinical translation, are reviewed, and direction for future perspectives is provided.

Keywords

brain activity mapping (BAM); nanoneuroscience; nanoneurotoxicity; neural regeneration; neuroimaging; optogenetics

1. Introduction

Neurons form the basic building blocks of the nervous system. The coordinated firing activity of a large number of neurons results in functional circuits in the brain[1] However, the nervous system is susceptible to disease and injuries such as cancer, traumatic brain injury and neurodegenerative diseases. Current strategies, which include drugs, chemotherapy, radiotherapy and surgery, are only partially useful as mortality rates remain high. Moreover, if the patient survives, the quality of life that follows is unsatisfactory. These challenges are due, in part, to the lack of effective and optimal therapy, but more fundamentally to the lack of understanding of the very thing that constitutes the nervous system: neurons and their functional circuits.

To cure disease, the cause of disease must first be understood. In the case of the nervous system, the neuronal circuits and their functions must be considered before all else. Elucidating brain circuitry and function is a conundrum that has eluded scientists for more than 100 years and represents one of the greatest challenges faced by the scientific community. Traditional methods rely on electrodes for studying neuron activity in brain function but are limited in being able to sense only a few neurons in isolated brain regions, whereas neural circuits involve millions of neurons arranged in a complex level of

organization.[1,2] This organization is due to the emergent nature of neural function, which arises from intricate interactions between the constituents of the neural circuit.[1,3] Further adding to these complexities is the plasticity of neurons, which undergo dynamic spatiotemporal rearrangements. These complexities have motivated scientists to develop strategies to gain deeper knowledge of brain circuitry.

One such strategy is the Brain Activity Map (BAM) Project, an international initiative aiming to "record every action potential from every neuron within a circuit" to aid the reconstruction of complete neural circuits.[4] By recording the patterns and sequences of the firing of individual neurons, a dynamic map of the functional connectome can be constructed to aid our understanding of the regulation of mental and behavioral states.[5] Since the announcement of the initiative, the growth of the neural circuitry field has escalated exponentially. This, in turn, has led to the growth of many different fields, including nanoneuroscience.

As suggested by its name, nanoneuroscience is the marriage of the fields of nanotechnology and neuroscience. Nanotechnology has shown promise for a variety of biomedical applications.[6] and the recent intertwining of both fields has given rise to what may be solutions to some of the biggest conundrums in the scientific community. A selection of the current applications of nanotechnology in nanoneuroscience-related fields is presented in Table 1.

The collaboration of the two fields has already changed the landscape of diagnostics and therapeutics in the nervous system. These successes prove that nanoneuroscience, if studied further, holds promise to deepen our understanding of neural circuitry and therefore contribute to initiatives such as the BAM Project.

The potential applications of nanoneuroscience provide a valuable route for further research in miniaturization and performance improvement of small artificial devices, such as nanodevices for neural interfaces.[7] For example, the collaboration between nanomaterial science and neural prosthesis technology brings about vast possibilities for safer and improved brain implant treatment in patients suffering from neurological conditions such as paralysis, blindness and epilepsy. Additionally, a deeper understanding of the formation and transmission of neuronal signals on the cellular level, with the aid of nanotools, can further improve the design and development of brain-inspired computing, a new computing system based on recent interdisciplinary progress.

However, as a consequence of the complexities of neuronal cells and the mammalian nervous system, in addition to the limited number of nano-neurotoxicology studies, the clinical applications of nanotechnology in neuroscience remain in the early stages of development. Despite these barriers, expanding multidisciplinary teams in the field of nanoneuroscience, including engineers, physicists, material scientists and clinicians, have helped to propel the field of nanoneuroscience to greater heights.

This review summarizes the basic concepts associated with neuroscience and the current journey of nanotechnology towards the study of neuron function by addressing various concerns on the significant role of nanomaterials in neuroscience and by describing the

future applications of this emerging technology. The main focus of this article is to review the implications of these recent findings and raise future research directions to develop nanoscale materials for the advancement of neuroscience applications. Nanoneuroscience is an emerging field that can greatly impact the understanding of neural circuitry and neurological treatment.

1.1. Thinking Big with Nanoneuroscience

Nanotechnology refers to the study of nanomaterials that include biological and non-biological structures. Due to their size of 1–100 nm, nanomaterials possess unique chemical, electrical, magnetic, mechanical and optical properties that confer advantages over traditional materials.[8] Compared to the traditional sciences, nanotechnology is a relatively new field. The founding of nanotechnology can be traced to as early as 1959, when Richard P. Feyman laid down the conceptual foundations of the field of nanotechnology in his seminal lecture "[There's] Plenty of Room at the Bottom". In 1974, Nori Taniguchi became the first person to define the term "nanotechnology".[8] Subsequent phenomenal advancements have impacted the field of medicine, thus leading to a demand for attention from multi-disciplinary teams comprising engineers, physicists, material scientists and clinicians.

"Nanoneuroscience" is a science that bridges neuroscience and nanotechnology (Figure 1) by concurrently addressing the fundamental goals of these two separate fields. Nanotechnology is the science that deals with materials at nanoscale levels, and the collaboration of this field with bioengineering and neuro-science can transform basic science into novel materials and devices for the treatment and monitoring of the pathological condition of neurological disease. The main goals of this technology are to understand how the nervous system operates and how neurons communicate and organize themselves into ordered networks in various action and mental states to treat the disease related to nervous system.

The collaboration between nanotechnology and neuroscience, though still at the early stages, utilizes broad concepts, such as drug delivery, cell protection, cell regeneration and differentiation, imaging and surgery, to give birth to novel clinical methods in neuroscience (Figure 1). The potential applications of this union are not limited to those named above, as the assimilation of nanotechnology into optogenetics and the piezoelectric effect further indicates its prospective applications in neuroscience. Ultimately, the clinical translation of nanoneuroscience implicates that central nervous system (CNS) diseases, including neurodevelopmental, neurodegenerative and psychiatric diseases, have the potential to be cured, while the industrial translation of nanoneuroscience indicates the need for advancement of brain-computer interface technologies.[9]

The evolving areas of nanoneuroscience have recently opened doors to a multitude of possibilities for neuroscientists to contribute to a deeper understanding and investigation of neuronal function associated with brain disease. Nanoscience has provided vast hopes for the medical sciences in comparison with the classic techniques of pharmaceutical drug design and development.[10] Nanoscience has also permitted the advancement of

nanomedical devices for use in the diagnosis, monitoring, prevention and treatment of pathological conditions.

This newfound hope for the medical sciences is due in part to the development of nanotechnology that can be manipulated and controlled by nanometer-scaled physiochemical processes within the body. In terms of the design and development of pharmaceutical drugs, large molecular databases can be scanned to identify specific proteins in damaged neurons that must be targeted to restore nanomechanical function.

2. Properties of Nanomaterials for Neuroscience

The CNS is a highly guarded sanctuary, which complicates the diagnosis and treatment of CNS disorders. The blood-brain barrier (BBB) prevents larger molecules from penetrating the brain.[11] This restricted anatomical access makes diagnosis and treatment more difficult compared to other disease sites. Consequently, drug treatment of CNS disorders via systemic administration is often inefficient. The heterogeneous cellular and molecular environment, complex anatomical and functional “wiring”, and complicated information processing further add to this challenge.[12] In response to these difficulties, an increasing number of groups are investigating the properties of various nanomaterials to exploit the inherent advantages of their nanosize. Several essential properties and factors that make nanomaterials ideal for neuroscience are discussed in this section.

Nanomaterials reflect the surface properties of organic tissues, such as topography and energy, more accurately than their conventional, micrometer-scale counterparts. Furthermore, due to their small size and advancements in synthesis methods, nanomaterials have many advantageous traits, such as high surface area-to-volume ratio, multi-functionality, site-specific delivery or targeting, controlled release and versatility in enabling surface modification.[13] These traits could help enhance the resolution and sensitivity of diagnostics, minimize side effects through targeted therapy and regulate therapeutic effects by controlling drug release in a specific environment. Therefore, nanomaterials can be used as vectors for drug delivery, as strategies for neuroprotection, as scaffolds for neuroregeneration and differentiation, as modalities for neuroimaging and as devices for neurosurgery.[14]

Recently different types of nanomaterials (organic/inorganic NP systems) (Figure 2) have been used in the field of nanoneuroscience, and their potential applications have been governed.[15] The structural and functional properties of these nanomaterials and their potential clinical applications in neuro-science are summarized in Table 2.

Multifunctional nanoparticles (MFNPs) have massively evolved as a new research area that can be tailored to possess specific functionalities and therapeutic solutions.[73] The diversity of structures in which MFNPs can participate is huge, as reflected by the ever-growing pool of nanomaterials with unique conductive, thermal, mechanical and toxicological properties.[74] These MFNPs can take the form of porous or non-porous and spherical or filamentous structures. Despite the wide variety of materials and structures used to construct MFNPs, they generally share similar principles.[74] A typical schema of a MFNP might involve an

imaging domain such as a fluorescent probe, a targeting molecule such as a targeting ligand to bind to receptors expressed on cells, and a molecule to be delivered such as a drug or gene.[75] These components functionalize the NPs, hence the name "multifunctional nanoparticle", and can be either embedded within a porous matrix or chemically bonded ligands that are readily functionalized upon integration with the target system.[76] Given the wide array of biophysical properties and core material combinations available and the number of structural permutations a given NP may assume, MFNPs can theoretically cure a large range of diseases in any biological environment in a site-specific and cell-targeted fashion.

Shape is an important factor that has a substantial impact on drug delivery in terms of pharmacokinetics and BBB penetration, with a factor-of-10 difference in half-lives between spherical and filamentous nanomaterials.[77] Hence, nanomaterial shape is a critical factor when choosing a vector. The system into which nanomaterials are introduced also plays a key role in governing the dynamics of cell-particle interactions and, as a result, toxicological effects. Numerous studies have already demonstrated that biological agents, particularly microbial species, can influence nanomaterial stability either antagonistically or, in some instances, cooperatively.[78]

Awareness of system-particle interactions is particularly important in the therapeutic context, as MFNPs are likely to be introduced into systems in a pre-existing disease state. Although content formulations impact structural properties, biological properties are more strongly influenced by surface chemistry, which is not always straightforward to analyse. Nonetheless, expanding our knowledge of the pharmacodynamics and pharmacokinetic properties of such interactions may facilitate the development of a platform for the future technologies, which will likely rely heavily on influencing native biological function itself by directing neuronal growth or affecting stem cell differentiation.

No one MFNP system is ideal, as the properties of a NP depend on a combination of factors including surface functionalization, formulation, shape, size and the environment in which the NP is introduced. These considerations must be included when designing MFNP systems.

3. Diagnostic and Therapeutic Applications of Nanotechnology in Neuroscience

In this section, we aim to describe the diagnostic and therapeutic applications of nanotechnology in neuroscience by describing the main principles, concepts and strategies. This broad approach to understanding the applications of nanotechnology in neuroscience will increase the applicability of the knowledge to various CNS diseases, as these general principles are not limited to specific scenarios. Nanomaterials for diagnostic and therapeutic purposes, or 'theranostics' when they possess a dual function, including drug delivery, neuroprotection, neural regeneration, neuroimaging and neurosurgery, are critically appraised in this section.

3.1. Potential Applications of Nanomaterials for Drug Delivery to the Central Nervous System

The BBB restricts the entry of the majority of small molecules and macromolecules into the CNS.[11] This renders traditional systemic administration of most drugs ineffective. However, the applications of nanotechnology to drug delivery have been widely studied in vitro and in preclinical assessments and provide alternatives for the treatment of CNS disorders. Currently, there are four main ways to deliver drugs to the CNS: i) invasive delivery; ii) pharmacological approach (free passive movement of drugs across the BBB due to their small molecular size, low hydrogen bonding capacity and low lipophilicity, e.g., reduction of the number of polar groups, which increases drug transfer across the BBB;[79] iii) temporary disruption of the BBB; and iv) nanobased drug delivery systems.[80] Invasive delivery is only reserved for selected cases and is not efficient against brain metastases or neurodegenerative diseases, which require therapeutic agents to be delivered throughout the brain.[11] The reversible opening of the BBB via osmotic or chemical strategies does allow therapeutics to cross the BBB but can result in significant damage to the brain.[81] A less invasive option is the systemic administration of drug delivery systems to penetrate the vasculature of the brain. This can be achieved by using nanomaterials as transporters or carriers to improve lipid solubility and mask any drug properties that prevent crossing of the BBB.[82] NPs such as nanoliposomes, micelles, nanogels and dendrimers are examples of some technologies that have been employed for this purpose.

Nanoliposomes are perhaps some of the earliest nanomaterials engineered for drug delivery.[83] These vesicles are composed of an aqueous core and one (unilamellar) or several (multilamellar) lipid or phospholipid bilayers. Conventional liposomes are cleared from the circulation via the reticuloendothelial system (RES). However, the circulation time can be extended through particle size reduction (<100 nm) and surface modification with polyethylene glycol (PEG). Liposomes can be functionalized with monoclonal antibodies, which act as targeting ligands to enable receptor targeting to receptors expressed on tumour cells. Liposome constructs functionalized with peptides specific to nicotine acetylcholine receptors on the BBB have been successfully used to deliver drugs such as doxorubicin, a chemotherapy drug, to glioma cells in an animal model.[84] The ability to multifunctionalize nanomaterials to achieve targeted therapy is perhaps one of the greatest advantages of nanotechnology, as it can potentially eliminate systemic toxicity, a conundrum in current chemotherapy.

Apart from the aforementioned ligand-receptor strategy, targeted therapy has also been achieved using magnetic nanoparticles (MNPs).[85] MNPs are usually composed of iron oxide. A magnetic field is externally applied to steer the MNPs to the desired site. Proof-of-concept has been shown, and the strategy has found success in the delivery of brain-derived neurotropic factor (BDNF) across the BBB for neuroprotection.[86]

While cell targeting is critical in successful chemotherapy, another important factor for effective drug delivery is the pharmacokinetics of the nanomaterial. Micelles, which are aggregates of amphiphilic molecules that consist of a hydrophobic core stabilized by a hydrophilic shell, can promote desirable pharmacokinetics. In aqueous solutions, micelles form spontaneously with the hydrophilic shell exposed to the surrounding environment and

the hydrophobic core sequestered within. Drugs that are insoluble or poorly soluble in water can be incorporated into the hydrophobic core to help improve bioavailability and stability. Using peptides as the targeting ligand, a micelle construct was successfully used to deliver a platinum-based chemotherapy drug to glioblastoma through the BBB, exhibiting properties of stability due to high levels of accumulation at the tumor site in an animal model.[87]

Additionally, successful drug delivery is highly dependent on the rate of release of the drug from its carrier. Nanogels, which are hydrogels composed of cross-linked ionic and nonionic polymers, can permit steady, controlled drug release.[88] One such use of nanogels to control chemotherapy drug release was the administration of methotrexate-loaded chitosan nanogels in rats, which resulted in a slower and steadier rate of drug release compared to free methotrexate.[28] Shape also plays an important role in drug delivery. Dendrimers have a spheroid nanostructure consisting of a repetitively branched 3D structure that can be grown from one or several cores. This controllable unique structure enables the encapsulation of drugs. Dendrimers consist of three architectural domains: the core to which branches are attached to, the shell of branches that surrounds the core, and the multivalent surface formed by the terminal branches.[89] Compared to most nanomaterials, dendrimers are smaller in size and have a lower polydispersity – a measure of the distribution of molecular mass in a given polymer sample.[90] Consequently, studies have been widely performed to investigate the use of dendrimer conjugates with chemotherapy drugs to achieve intragliomal delivery.[91]

One issue worth noting is that NPs can be neurotoxic or cause permanent alterations to the BBB.[92] This could lead to potentially fatal consequences, such as brain tissue oedema or the entry of toxins and molecules that are normally prevented from CNS entry. The future is bright, however, for researchers investigating new BBB shuttles, such as lipid-core nanocapsules (LNCs), to treat devastating neurological diseases such as glioblastoma. For example, rhodamine 6-labeled LNC drug shuttles were designed to deliver drugs across the BBB and into brain tissue with high efficiency, thus reducing glioblastoma after oral or intravenous administration.[22] Additionally, several notable examples of “nanomedicines” have been translated from bench to bedside, including liposomal Doxorubicin and Doxil.[93] Nanomedicine-based drugs in clinical trials or that have been clinically approved for the treatment of diseases related to the nervous system are shown in (Table 3). However, further long-term in vivo studies are needed to establish any neurotoxic effects and to develop strategies to circumvent potential toxicity issues.[94]

3.2. Nanomaterials for Neuroprotection

Traumatic brain injury (TBI) is trauma to brain tissue due to hypoperfusion and hypoxia, which can lead to ischemia and infarction. Reperfusion injury is the damage caused to tissue when the supply of blood returns to the brain after a period of ischemia. These injuries are major epidemiological concerns because they cause significant disability and even death. Neuroprotection refers to the mechanisms or strategies used to slow disease progression by halting or slowing further neuronal loss. Such strategies include mitigating oxidative stress, introducing growth factors, introducing anti-apoptotic peptides, and reducing excitotoxicity and neuroinflammation.[98]

Oxidative stress is thought to be the key neuropathological process contributing to further neuronal loss after CNS insults.[99] One approach to mitigate these effects generally involves the use of nanomaterials loaded with antioxidants, such as catalase and superoxide dismutase, to eliminate reactive oxygen species (ROS), the culprit of oxidative stress, and its mediated effects such as the inflammatory cascade and neural degeneration.[100] Nanomaterials with antioxidant properties, such as cerium oxide NPs, can also preserve endogenous antioxidant systems.[101]

A nanopolymer-based platform that can react with oxygen known as an oxygen-reactive polymer (ORP) can be used in diagnosis and therapy to reduce the production of ROS in brain trauma. The designed ORP contains mostly PEG by mass to increase the half-life during circulation and biocompatibility. Gadolinium is provided as a contrast agent for magnetic resonance imaging (MRI). By mole, the OPR is mostly a thioether-containing unit used for ROS scavenging (Figure 3A). The OPR can scavenge ROS, reduce secondary injury in a controlled cortical impact (CCI) mouse model with TBI, and accumulate in damaged areas of the brain (Figure 3B,C,D).[102]

To prevent further neuronal loss, mechanisms must be installed to prevent cell apoptosis and encourage cell regeneration. This provides a rationale to introduce anti-apoptotic and growth factors to cells. Anti-apoptotic and growth peptides have been shown to be neuroprotective in stroke models.[103] Chitosan NPs loaded with basic fibroblast growth factor (bFGF) and small peptide inhibitor of caspase-3 (z-DEVD-FMK) produced a significant reduction in infarct volume.[104] This reduction was, in part, also due to the functionalization of the nanoparticle with antibodies against the transferrin receptor-1 on the BBB endothelium to enable receptor-mediated transcytosis across the BBB. Taken together, the effects of the added factors demonstrated the usefulness of NPs as a vehicle for the delivery of therapeutics across the BBB for neuroprotection against TBI.

Neuroprotection strategies may also be indicated for neurological injury following cardiac surgery, particularly after hypothermic circulatory arrest (HCA).[105,106] In a canine model, excitotoxicity and neuroinflammation were shown to be the key mediators of post-HCA neurological injury.[107] High doses of valproate confer some degree of neuroprotection but are associated with adverse side effects.[108] Consequently, the use of systemic polyamidoamine (PAMAM) dendrimers conjugated with *N*-acetyl cysteine (NAC), which attenuates neuroinflammation, and with valproate, which attenuates excitotoxicity, was explored in a rabbit model. Preliminary results showed that the dendrimer conjugates conferred neuroprotection but with improved biodistribution and significantly reduced side effects compared to valproate alone.[106]

Recently, with the development of self-assembling peptide nanofiber scaffolds (SAPNS), a new protective, therapeutic strategy for intracerebral haemorrhage (ICH) has emerged. One study evaluated ICH-related brain injury and functional recovery by observing the effects of hematoma aspiration and intrastriatal administration of RADA16-I. Intracerebral delivery of SAPNS into the haemorrhagic lesion of a rat model of ICH replaced the hematoma and reduced acute brain injury. With SAPNS functioning as a biocompatible material in haemorrhagic brain cavities, the formation of brain cavities was reduced, and an

improvement in recovery of sensorimotor function was also observed. The local delivery of SAPNS as a treatment for ICH-related brain injury may allow better repair of ICH brain damage and improved recovery rates.[109]

Patients suffering from neurodegenerative diseases may also benefit from neuroprotective strategies utilizing nanomaterials. Alzheimer's disease is a devastating neurodegenerative disease characterized by toxic amyloid beta protein (Aβ) aggregates. An interesting neuroprotective technique with the potential to aid the prevention and decrease the progression of Alzheimer's was demonstrated by Kogen et al. in their use of gold nanoparticls (AuNPs).[110] AuNPs linked to the peptide H-Cys-Leu-Pro-Phe-Phe-AspNH_2 (Cys-PEP) were synthesized to allow the NPs to selectively attach to the Aβ aggregates. After conjugation, weak microwave fields were applied to the AuNP system, which in turn absorbed the radiation and released energy. This caused the amyloid aggregates to disaggregate. Given the strong link between Aβ aggregates and Alzheimer's, this method, along with more extensive animal studies, could lead to a very promising neuroprotective strategy to fight this devastating neural disease.

The various strategies available for neuroprotection imply that there is considerable opportunity for the development of different nanomaterial platforms. However, the toxicology profiles of these nanomaterials require greater attention because it is difficult to ascertain if toxic effects are due to the pre-existing pathological processes or the nanomaterial itself.

3.3. Nanomaterial-based Approaches for Neural Regeneration

One of the fields most closely allied with nanotechnology is regenerative medicine. Efforts to incorporate nanomaterials in tissue engineering have highlighted superior mechanical, catalytic, conductive, optical, magnetic and cytocompatible properties compared to traditional materials, and much promise has been shown in engineering biocomposites for neural tissue.[111,112]

Achieving functional CNS repair in instances of trauma and neurodegenerative disorders, such as Alzheimer's and Parkinson's disease, remains the holy grail of neural regeneration research. The main obstacle to traditional cell therapy and implantation techniques is that the CNS environment, in contrast to the periphery, is not conducive to regeneration.[113] This shortcoming is due to a complex combination of glial and extracellular factors, both constitutive and induced in response to injury. Such elements include local requisitioning of myelin-associated inhibitors, such as myelin-associated glycoprotein (MAG), mediator-fuelled NOGO pathway activation and upregulation of latent matrix proteoglycans.[114] The culmination of these inhibitory factors is delayed Wallerian degeneration in response to injury and the development of glial scar tissue instead of functional tissue, thus preventing proximal axon re-growth and stymying nascent cytoarchitectural regeneration.[115]

Facilitating repair in such a non-permissive environment poses a stark challenge that demands materials with exceptional properties in at least three distinct areas: i) cytocompatibility; ii) mechanical properties; and iii) electrical conductivity.[116] Cytocompatibility is fundamental in promoting appropriate neural growth without eliciting

aberrant inflammatory or infective processes. Strong mechanical properties are critical, as any scaffold or microfixation devices must provide adequate physical support to aid neural tissue formation. Electrical conductivity may also prove a decisive factor, as electrical stimulation may be used to guide the process of neural regeneration, effectively superimposing an external driver for Hebb's Law, which states that "Neurons that fire together wire together", to stabilize appropriate synaptic connections and disavow aberrant ones, thus mimicking or enhancing activity-dependent synaptogenesis.

Various conventional materials, both natural and synthetic, have been adopted under these principles.[112] However, many still exhibit shortcomings at the point of application. Autografts are difficult to collect in sufficient quantities from patients and exhibit a theoretical risk of impairing donor site nerve function.[117] Allografts may frequently induce local inflammation, suffer rejection or present a risk in disease transmission, thus leading to a high failure rate among implants.[118] Attempts to utilize traditional synthetic biomaterials, such as silicon probes, in neuroprosthetic devices and polymers used as nerve conduits have been frustrated by extensive glial scarring proximal to the implanted material,[119] which then exhibits non-optimal mechanical and electrical properties for inducing growth. Amidst this shortage of success, nanotechnology presents a previously untapped source of potential in developing novel and superior neural tissue engineering materials and therapeutic strategies for CNS repair.

Chief among these is the rapid development of nanotube scaffolds; with their extraordinary conductivity properties, such structures offer to support and possibly even enhance native electrochemical activity by boosting the regenerative potential of the implant site. Physically, these materials also mimic the tubular structures of axons and dendrites. These ideas have been implemented by several groups who have turned to carbon nanotubes (CNTs) based on their combination of electrical conductivity, mechanical properties, and comparable nanoscale dimensions to organic neurites.[120] CNTs can be defined as cylindrical nanostructures composed of graphene sheets wrapped onto themselves and can either be single-walled CNTs (SWCNTs) or multi-walled CNTs (MWCNTs). CNTs can be functionalized with growth factors such as nerve growth factor (NGF) or BDNF to stimulate neuronal growth on the scaffold.[121]

To fully understand the potential of CNTs, the developmental history and progression of methods over the years must be appreciated. Mattson and colleagues were among the first to demonstrate the feasibility of growing neurons on MWCNTs. They observed a greater than 200% increase in total neurite length and an almost 300% increase in the number of branches and neurites on MWCNTs coated with bioactive 4-hydroxynonenal compared to uncoated scaffolds.[122] Expanding on this research, Hu et al. showed that neurite growth patterns (length, branching and number of growth cones) could be influenced through surface charge modulation achievable through chemical functionalization.[123] Lovat and colleagues lent credence to the conductivity properties of MWCNTs by demonstrating that purified MWCNTs potentially boost electrical signal transfer within neural networks.[124] Related works have focused on refining biophysical properties by offering different structural permutations. For instance, highly ordered, free-standing SWCNT matrices have been shown to be highly biocompatible, thus favorably inducing neuronal differentiation,

guided axonal growth and branch elaboration (Figure 4C).[125] In parallel, vertically aligned nanotube arrays have been developed to provide a natural and intimate neural-electrical interface between cells and fibers that also enhances tensile mechanical and electrical conductive properties.[126]

After validating the basic material properties, groups then shifted their research emphasis to more complex patterning of CNTs with synthetic or organic components, thus forming nanobiocomposites designed to achieve more specific goals. For instance, McKenzie et al. sought to suppress glial scar formation by incorporating different molecular weight ratios of high surface energy carbon nanofibers (CNFs) into composite polymers.[128] This was accomplished by managing the ratio between the molecular weight of the polymer and surface charge. This study successfully demonstrated that astrocyte adhesion could be effectively inhibited by a CNF/polymer composite. Sha et al. combined a polymer nanofiber scaffold with graphene oxide (GO) sheets for comparison with unaltered polymer nanofiber scaffolds (Figure 4D). The graphene-nanofiber hybrid scaffold promoted the growth of neural stem cells and also led to differentiation in neural stem cell lines, demonstrating that nanofiber scaffolds, in combination with different coating materials, can lead to better methods for neural tissue engineering.[127]

Furthermore, the properties of these nanostructured CNFs were associated with decreased astrocyte proliferation and decreased corollary glial scar formation.[128] Gabay and colleagues developed a novel strategy for fabricating neurite-attractive CNT islands on substrates and were able to pattern networks to their own pre-determined designs.[129] More recently, Sulejczak et al. demonstrated that, in addition to neurodegenerative diseases, CNTs can play a role in the restoration of neural pathways damaged by the excessive scarring that occurs after TBI. The implantation of an L-lactide-caprolactone copolymer electrospun CNF mat in a rat model of surgical brain injury helped delay and reduce glial scar formation and thickness.[130] Although many CNFs have proven to be biocompatible, further studies are needed to evaluate long-term effects and potential neurotoxicity.

An area of great promise is the marriage of CNTs and stem cell technology with the purpose of tackling neurological disorders. Although the concept of incorporating multipotent stem cells into nanoscaffolds has garnered much attention,[131] the effective delivery and selective differentiation of these cells to best assist regeneration remains uncertain. Although the underlying mechanisms have not been fully elucidated, evidence has shown that nanostructured materials may contribute to selective stem cell differentiation even in the absence of growth factors. For instance, Lee et al. injected CNFs embedded with stem cells into stroke-damaged rat neural tissue and found extensive differentiation with minimal glial scar formation in vivo;[132] Jan and colleagues successfully implanted a layer-on-layer SWCNT-stem cell composite that achieved favorable differentiation of mouse embryonic stem cells into neurons, demonstrating that the composites produced more neurons and fewer astrocytes during a seven-day culture period than poly L-ornithine controls.[132]

In a relatively recent study, improved differentiation of neural stem cells (NSCs) into neurons was achieved by utilizing silica NPs to aid the delivery of select siRNAs, which induce RNA interference (RNAi).[133] This nanotopography-mediated reverse uptake

(NanoRU) delivery platform consisted of a silica NP monolayer coated with the desired siRNA and extracellular matrix proteins. The siRNA on the silica NPs induces the knockdown of the transcription factor SOX9, which determines neuronal or glial fate in NSCs, thus forcing the NSCs to differentiate into the desired neurons. Notably, the size of the silica NPs was an important factor in gene knockdown. To quantitatively study the knockdown abilities of this RNAi and silica NP system, NSCs genetically modified to encode GFP were examined. The platform with the smallest NPs showed the highest knockdown, whereas the largest NPs showed the lowest knockdown (Figure 5). These data are indicative of the possibility that utilizing smaller silica NPs in this platform may permit more controlled differentiation of NSCs to neurons.

It is increasingly clear that CNTs and several other composite materials may have a role in determining effective delivery and the favorable differentiation of NCSs. However, efforts to elucidate the mechanisms underlying these processes and their activation may open the door to ever more effective scaffold designs and ultimately pave the way for effective CNS repair.

3.4. Applications of Nanotechnology for Neuroimaging

Nanotechnology permits the visualization of experimental data through optical imaging, resulting in greater spatiotemporal accuracy and resolution than ever before. One conceptual framework is the functionalized semiconductor nanocrystals known as quantum dots (QDs). These are nanometer-scaled particles that exhibit quantum mechanical traits including electrical, thermal and optical properties that differ substantially from those of the bulk materials. Physically, they comprise a heavy metal core (cadmium-selenium or cadmium telluride), an intermediate unreactive zinc sulphide shell, and an outer coating that can be engineered to meet a specific functional demand by appropriating the surface chemistry of specialized bioactive compounds.[134]

Given the increasingly challenging demands on traditional organic dyes, investigations have focused on the characteristic quantum mechanical properties of semiconductor nanocrystals.[135] Functionalization of QDs with conjugated fluorescent proteins holds substantial advantages over conventional fluorophore-based fluorescence visualization techniques. In addition to evading the stability problems associated with fluorophores and undergoing minimal photobleaching, QDs also exhibit dramatically enhanced signal detection. Their broad absorption spectra but narrow emission spectra are manifested in a high extinction coefficient for a comparable quantum yield, greatly increased signal-to-noise ratio and, consequently, brighter signal.[38,136] To offer some parametric context, estimates suggest that this combination of physical and optical factors result in QDs that are 20 times brighter and 100 times more stable than traditional fluorescence vectors.[39]

QD labelling has already found broad applications in vitro for diverse and varied cell types and has shown shows utility in single-particle tracking within live cells.[137] However, advances in the labelling of neural tissue have been slower. Care must be taken to not fall prey to the tacit assumption that results for other cells will also be applicable to neurons and glia. Nonetheless, tentative advances have been made, particularly in characterizing the dynamics of neural receptors. Dahan et al. demonstrated the capability of QDs in achieving single-particle tracking over periods ranging from seconds to minutes, facilitating analysis of

spinal glycine receptor diffusion in real time.[138] In a separate neurophysiological experiment, immobilized QDs were conjugated with B-nerve growth factor (BNGF) and shown (Figure 6) to interact with TrkA receptors in PC-12 cells, a cell line derived from rat pheochromocytoma.[139] Such proof-of-principle experiments will pave the way for more extensive adoption of QDs in future neuroscientific protocols.

The potential for QDs is expansive and ever-growing. New functionalization and labelling methods to better target surface proteins or promote their superior solubility characteristics have been developed and assessed using labelled AMPA receptors[140] and by measuring the cytotoxicity of hippocampal neurons,[141] respectively. The majority of neuroscientific QD ventures are ex vivo studies, but several groups have pioneered their application in vivo using QD immunoconstructs conjugated with Ri7 antibodies, thus targeting the murine transferrin receptor on the mouse BBB.[142] To take experiments from the petri dish to in vivo systems in the mainstream may require a greater focus on addressing the issue of toxicity. Although QD technology exerts minimal cytotoxicity in vitro, in vivo applications present a far more dynamic challenge in terms of long-term cytocompatibility and system reactivity. Addressing these safety issues will be essential for taking QD-labelling techniques to the next level.

Utilizing nanomaterials for optical imaging also holds promise for better visualization of brain injuries, such as TBI. Necrotic cells in the brain during TBI were targeted using PEGylated poly (lactic-co-glycolic acid) (PLGA) NPs encapsulating both perfluorocarbons (PFCs) and near infrared (NIR) fluorophores. The NPs were combined with cyanine dyes, such as IRDye 800CW, and then traced using optical imaging and fluorine magnetic resonance imaging (^{19}F MRI). The imaging of PLGA NP(NIR700 + PFC)-PEG-800CW NPs showed that they accumulated in blood pool areas for increased durations and were successful in targeting traumatic brain injury-damaged tissues. The ability of these necrosis-targeting NPs to provide quantitative 3D information on deeper tissues through MRI and rapid qualitative optical monitoring of TBI give them potential for use in clinical diagnosis of brain injuries.[143]

Nanotechnology is not limited to optical imaging techniques. One of the key objectives of neural tissue engineering and stem cell technology at large is developing minimally invasive means of tracking transplanted cells over long periods to monitor their performance in vivo and in situ. Magnetic resonance imaging (MRI) is already a mainstay of noninvasive and radiation-free in vivo imaging. It is conceptually intuitive that in conjunction with nanotechnology, MRI offers a feasible, high-fidelity means of tracking transplanted targets.

Superparamagnetic iron oxide (SPIO) NPs and ultrasmall superparamagnetic iron oxide (USPIO), which are types of MNPs, have already been co-opted as contrast enhancers, and current investigations in neuroscience are focusing on how iron oxide-labelled stem cells/progenitors can contribute to our understanding of neurological disease.[144] By elucidating critical events in cell migration and differentiation in animal models, it is hoped that such studies might inform future transplant protocols, thus helping to determine optimal timing and location. The introduction of USPIO into human foetal neural precursor cells (hNPCs) in vitro was not only visualized well on MRI but was also not biologically detrimental to the

cells in terms of cell viability, cell cycling, proliferation, apoptosis, migration, lineage potential and intracellular calcium concentration.[145] In addition, the MRI visualization was dose-dependent, further supporting the role of USPIO in imaging. Another study using SPIO labelling of hNPCs in vivo, however, found that it was not a viable imaging technique as it could not determine graft rejection in vivo, which is of utmost importance in understanding cell behavior post-transplantation.[146] This highlights the variability in the results of in vitro and in vivo studies, concordant with the known complexity of biological systems.

Although a clinical study utilizing SPIO-labelled mesenchymal stem cells in two patients with neurological disease has been reported (Figure 7),[147] several challenges must be met to take this technology further. A preliminary step involves appropriately addressing safety concerns, specifically, the use of SPIO NPs as intracellular contrast agents. A sophisticated framework for assessing and approving novel nanomaterials as medical products may be required.[148] A further obstacle is synthetic rapidity. Labelling must be readily achievable within a set timeframe to maximize its utility, particularly if nanomaterials are to be introduced in clinical trials in which cells are used in patients within 24 hours of isolation. A rapid method of labelling has been reported by Kim and colleagues using SPIO NPs coupled with 2-aminoethyl-trimethyl-ammonium (TMA) to form SPIO-TMA. Not only is this method quick and effective, but it also obviates the need for a transfection agent, thereby avoiding complications with vector internalization and additional safety concerns.[149] In another study, Liu et al. reported a new method for the preparation of SPIO-labelled mesenchymal stem cells (MSCs) that similarly does not require transfection agents or electroporation to verify whether transplanted cells have reached the target site and elicited their intended effects.[42]

Despite their unique combination of properties for tackling the challenge of transplanted cell-tracking in vivo, there are several notable limitations to the utilization of MNPs for neuro-imaging that must be addressed. One concern is the duration of time SPIO-labelled cells can be effectively tracked. Proliferation of pre-labelled cells in situ implies a problem of particle dilution. This is not an easy query with a simple solution, as studies have suggested a wide range of SPIO concentration half-lives ranging from 15 minutes to 18 weeks in vivo.[42,150] Another issue is the considerable loss of cell density over time, which manifests as a gradual attenuation of the MRI signal.[150] Improving spatial resolution under these conditions is most logically achieved through stronger magnetic fields, but the potential hazards of higher field strengths will pose a problem. Furthermore, the indirect nature of measurement means that there is not a simple correlation between the magnetic resonance output and the number of cells. Perfluoropolyether NP technology offers a way around this problem because these particles can be detected directly by ^{19}F imaging.[151] Studies are required to evaluate the cytocompatibility of this technology before it is offered as a feasible alternative. Finally, a principle that applies widely across the field of imaging as a whole is that no single visualization modality offers all answers. Hence, to track characteristics such as cell differentiation and function, it is likely that developments in complementary imaging techniques, particularly positron emission tomography and optical imaging, will function alongside SPIO-labelling to provide a nuanced and conceptually valuable picture of stem cell transplantation and in situ dynamics.

3.5. Nanotechnology in Neurosurgery

Neurosurgery has been used to treat CNS and peripheral nervous system disorders for years, but the introduction of nanomaterials brings about vast possibilities for advancement in the field. With the use of nanomaterials, new therapeutic strategies in neurosurgery have the potential in improve patient prognosis and quality of life. Some areas of interest in nanomaterials within the context of neurosurgery include nano-electromechanical systems (NEMSs), laser-associated vascular anastomoses, nanoscaffolds for neural regeneration, biocompatibility of surgical prostheses and nanowires.[152,153]

Neurosurgery requires the highest level of precision, as the brain is the control center for many vital functions, including cardiorespiratory regulation, metabolism and homeostasis. It is therefore desirable to remove as much unhealthy tissue and preserve as much healthy tissue as possible. Attaining this goal requires not only a skilled surgeon but also precise and accurate equipment to a nano-scaled degree. One promising recently developed NEMS is the 'NanoKnife' used in irreversible electroporation (IRE), a novel non-thermal ablation technique. Although the use of the NanoKnife had been investigated in solid tumors at other sites, it had not been used in the brain until a group used the NanoKnife in dogs with intracranial glioma.[154] The NanoKnife system consists of a generator using low-energy direct current that operates outside the sterile surgical field and a single-use disposable electrode probe, which is essentially used as the 'scalpel'. Pulse delivery is monitored and suspended if it exceeds 50A at any point. The NanoKnife was indeed capable of excising the tumor. However, the mixed response and survival rates among the dogs indicate that more work is needed to minimize side effects and, ultimately, death. The varied results might be attributable to the pulse dose, normal complications from surgery and craniotomy, such as aspiration pneumonia, and effects of adjunctive radiotherapy.[154] For tumors in key regulatory areas such as the brain stem, increased precision of the removal of the tumor may decrease unwanted side effects. In addition to tumors, the nanoscale precision of the NanoKnife could also potentially be beneficial in epilepsy surgery as it would allow surgeons to remove, with better precision, individual white matter bundles, the pathological process in epilepsy, and thus potentially allow improved outcomes.[152]

In neurovascular disease, such as aneurysms, temporary coronary occlusion is indicated while connecting the anastomosis. However, this poses a risk of ischemia and potential tissue damage. In response, the Excimer laser assisted non-occlusive anastomosis (ELANA) technique has been developed.[155] As its name suggests, ELANA uses laser catheters to punch a hole in the recipient artery, and thus temporary artery occlusion is not needed. However, lasers at high temperatures can cause damage to surrounding healthy tissue during tissue soldering.

An interesting nanomaterial that can be used in place of lasers is AuNPs, which have been shown to have excellent photo-thermal properties.[156] AuNPs can absorb light in the NIR region and convert the energy to heat. Their photo-thermal properties have been investigated in in vitro and in vivo studies using glioma cells and mouse models.[157] Taking it one step further, a group investigated the effect of AuNPs on the mouse brain vasculature.[158] The NPs were conjugated with VEGF ligand to target VEGF receptor-2-positive endothelial cells. The results showed that photothermal ablation was successful in vasculature disruption

using AuNPs.[158] The use of photothermal ablation by AuNPs, therefore, holds promise in neurovascular surgeries such as cerebral bypasses. The deep location of some vessels during these surgeries indicates the need for a small particle that can be manipulated and guided into remote areas, such as AuNPs. Therefore, using AuNPs or nanoshells and NIR light to perform vessel anastomoses would no longer necessitate temporary arterial occlusion, reducing the risk of ischemia.

Recently, a unique triple-modality magnetic resonance imaging-photoacoustic imaging-surface enhanced Raman scattering (SERS) nanoparticle (MPR) technique was developed that can accurately aid the delineation of the margins of brain tumors in experimental animals (Figure 8). Intravenous injection of MPRs into glioblastoma-bearing mice led to specific MPR accumulation and retention by the tumors and showed high picomolar sensitivity in all three modalities, thus allowing non-invasive tumor delineation. The greater precision of imaging enables improved surgical procedures.

Although the period during neurosurgery is challenging, the post-surgical period is equally if not more daunting. Axonal regeneration is necessary to limit functional disability, which is the main aim of neurosurgery. A few obstacles must be overcome post-surgery to achieve axonal regeneration: scar tissue formation after injury, gaps in nervous tissue and factors that inhibit axonal growth. SAPNS are a viable option to overcome these issues.[160–162] The role of a self-assembling peptide, RADA16-I, in supporting the reprogramming and maturation of human neurons was investigated. Self-assembling peptides can spontaneously assemble into nanofiber scaffolds when exposed to an appropriate chemical environment. This property was exploited for the purpose of neural regeneration, as evidenced by successful neurite outgrowth in both in vitro and in vivo transplantation.[161] The choice of culture is important. 3-D culture has many advantages over 2-D cultures (typically petri dishes, glass slides, multi-well plates) because a 3-D environment features extracellular matrix nanoscale fibers to allow cell attachment, growth, differentiation and communication.[161,162]

Another valuable use of nanomaterials in neurosurgery is to increase the biocompatibility of prostheses, such as implants for patients. Brain implants can stimulate the brain and help alleviate symptoms, such as tremors in Parkinson's disease.[163] Despite the promising results of implants, they are frequently considered foreign to the body and thus stimulate biochemical pathway cascades leading to complex molecular and cellular responses that can result in device failure.[164] CNFs, which can be used in brain implants due to their excellent conductive properties, minimize the functions of astrocytes. This is significant because astrocytes are the glial scar tissue-forming cells. Thus, CNFs can lead to a decrease in glial scar formation, which has potential to help maximize and lengthen the function of brain implants for patients.[128] Of note, limiting the development of the field is perhaps the range of ethical issues surrounding implantation of devices into the brain due to its inherent function, which controls cognition, behavior, motor and sensory systems[165] and, by extension, autonomy.

Furthermore, the integration of nanowires with cellular components creates a direct bridge between the cell and the environment within our immediate control, promising a means to manipulate cellular features with unparalleled precision–so long as the integration step can

be achieved and maintained without significant cell damage. Significant gains have already been made in demonstrating the safety of this technology at its most fundamental level. Yang et al. showed that mouse embryonic stem cells can be cultured successfully on silicon nanowires and that these wires can also be used as needles to deliver biological substrates such as green fluorescent protein.[166] Chen and colleagues similarly demonstrated the safety and efficacy of nanowire technology utilizing a fully re-purposed atomic force microscopy tip for the delivery of fluorescent NPs.[167] Notably, the tip diameter was less than 10 nm, and length scales substantially smaller than the cell were crucial to ensuring cell survival and effective substrate delivery. With further development and continued toxicology profiling, this technology could eventually aid nanosurgeries to cells within the CNS, alongside the study of the interface between neurons and neuronal implants in vivo.

The future of neurosurgery is bright. Neurosurgery patients in the future can expect to have more precise and less invasive treatment thanks to nanotechnology. Currently, researchers are developing nanorobots that can be controlled by surgeons to deliver precise treatment to patients.[168] These futuristic nanorobots may serve as actuators and/or sensors to be used in minimally invasive neurosurgery and provide extreme precision to surgeons. If delivered through the vascular system, these tiny robots can be nanomanipulated to detect pathology and diagnose problems from within the body.[169] One group has laid out how nanorobots should be integrated and developed so that they can be used for early intracranial prognosis of aneurysms.[170] Although not completely developed, the potential of nanorobotics in a neurosurgical setting is very promising. In looking to the future of nanomaterial research, neurosurgeons can look forward to providing even better care to their patients.

4. Future Developing Arenas in Nanoneuroscience

The BAM Project aims to map the neural activity of every neuron across all neural circuits with the ultimate aim of curing diseases associated with the nervous system. The announcement of this collaborative, public-private research initiative in 2013 by President Obama has driven the surge in developing methods to elucidate neural circuitry.[171] Three current developing arenas in the context of nanoneuroscience applications that will push such initiative forward are i) optogenetics, ii) molecular/ion sensing and monitoring and iii) piezoelectric effects.

4.1. Nanotechnologies for Optogenetics

In recent years, optogenetics has established itself as a powerful technology at the disposal of modern neuroscience.[172] At the heart of its utility lies an elegant concept envisioned by Sir Francis Crick more than three decades ago that we may selectively activate or inactivate neurons and a specific subpopulation of neurons within an in vivo network with the use of light in a binary fashion while leaving neighboring cells completely intact. Optogenetics not only succeeds in providing such a molecular scalpel–one that enables the dissection of neuronal systems into their functional constituents with unparalleled spatial, temporal, and neurochemical resolution[173]–but also allows us to reverse operations with a flick of a switch. So much of the historic progress of neuroscience has been dependent on chance and

grossly imprecise anatomic lesions, and the ability to engineer reversible knockouts at nanoscale level promises to revolutionize our understanding of the brain.

The scientific basis of optogenetics lies in the ability to selectively express ionotropic opsins, which are effectively light-gated proteins, within a genetically targeted subpopulation of neurons.[174] Light holds substantial benefits over other stimulus vectors; the precision with which it can be delivered in both spatial and temporal dimensions is unparalleled by any other chemical or biological agonist, as is its innate lack of gross invasiveness and homeostatic disruption. Furthermore, the rapid millisecond-scale on- and off-time kinetics of the opsin channels[175] facilitate high-resolution measurements of cascade output, while the reversibility of the effect facilitates repeatable measurements.[176,177] Taken together, these generalizable properties make optogenetics a potent tool for current goals to establish brain activity mapping[4] by enabling the stimulation of precise subsets of neurons in vivo, with the goal of establishing component function at a network level and functional-behavioral correlates at the top cortical level. Optogenetics currently finds widespread use in neuronal mapping as well as in eliciting and even correcting disease-related phenomena as varied as anxiety and depression,[178] retinal degeneration and regeneration,[179] memory and fear, [180] Parkinsonism[177] and social dysfunction.[181]

In combination with optogenetics, nanomaterials can play a significant role in discovering novel optical interfaces due to their unique properties, such as size, surface area, and quantum properties.[182,183] Additionally, in the case of plasmonic gold nanoparticles (PGNPs) a decrease in the size of NPs affects the surrounding environment's electromagnetic properties. By exploiting the unique, small size of PGNPs[184] and, in semiconductor nanocrystals, their[185] effect on the surrounding electromagnetic properties, neural activity can be stimulated.

The same group investigated the utilization of plasmon-mediated absorption of green wavelengths in PGNPs to generate local heating in cells. By generating local heating, thermally sensitive channels triggered action potentials. This method of generating action potentials in neurons is shown in Figure 9A,B. Carvalho-de-souza et al. also developed a technique involving surface functionalization of PGNPs to achieve maximum plasmonic absorption at 523 nm.[184] This heating of these PGNPs leads to a variance in membrane capacitance, which may be beneficial for optogenetics.

While much research in recent years has shown the effectiveness of optogenetics in stimulating neuronal activity, hurdles remain. One of the largest challenges in this growing research area is delivering visible light (~400–600 nm) to the desired neurons. Visible light is highly scattered in tissue, thus making it a challenge to deliver the required light to deeper neurons. One group utilized UCNPs to convert deep penetrating 980-nm NIR light into visible light with the ability to activate neurons optogenetically.[71] The group synthesized UCNPs consisting of a sodium yttrium fluoride (NaYF4) matrix that was co-doped with $Yb^{3+/}Tm^{3+}$. These NPs had an absorption peak at 980 nm and an emission peak in the blue-spectrum, which is effective for activation of light-sensitive ion channels such as channelrhopsin-2 (ChR2). These UCNPs were effectively combined with a polymer film to generate a biocompatible scaffold to optogenetically activate neurons (Figure 9C). This

novel research has future directions to permit optogenetic control of neurons at deeper locations within tissue.

Advances in nanotechnology will help us take optogenetics ever further. The coupling of the afferent, agonist delivery limb of the process, which is nanoscale engineering, with computational optics promises to deliver precisely modulated spatial light patterns,[186] opening up the possibility of stimulating specific, individual cells within the light-susceptible population. This would effectively provide an even greater degree of component control over the neuronal network, extending our reach beyond the limits of genetic targeting. At the effector channel level, the increasing understanding of molecular structure-function relationships is permitting the engineering of an ever greater diversity of NPs, with customized ion flow, spectral responses and channel kinetic properties.[174,187] At the very limits of this work, we can even begin to devise new classes of NP function. One example, elegant in its conceptual brilliance, is effectively 'running' Archaerhodopsin 3 (Arch) isolated from *Halorubrum sodomense* in reverse such that a membrane potential perturbation can elicit a change in the optical properties of the protein.[188] This microbial opsin thus becomes an unparalleled voltage sensor that is fully integrated within the neural network with optical levels of spatiotemporal resolution. This permutation of optogenetics succeeds in providing a means to map electrochemical activity from within the in vivo network, a long-held goal of electrophysiology in the context of neuroscience.

Although the light-activating dimension of optogenetics has received the greatest attention, the intrinsic labelling power of genetic targeting should be emphasized. Although isolated electrophysiological recording methods from nanoscale needle electrodes can provide high-fidelity readouts of multiple spike-firing units, they offer essentially no information on the genetic phenotype of the cells involved.[189] Theoretically, any combination of excitatory and inhibitory network components may be driving the overall spike train, thus providing only offer a very crude form of 'activity mapping' based on these methods alone. By adding an optogenetic input, i.e., by pre-implanting genetic control tools to generate their own spiking under sufficiently well-correlated light pulses, we can superimpose light-gated electrical activity onto the overall picture, allowing us to infer instances of shared identity from the resultant waveforms observed and thus assign a degree of genetic information to the population of cells under study.[189] By marrying electrophysiological recordings from nanoscale electrodes to optogenetic 'phototagging' techniques, we can begin to conceive a strategy for 'pure', genetically stratified, activity mapping of neuronal systems.

Optogenetics has huge potential but may not be the answer alone in the drive to achieve an all-encompassing map of the brain. Arguably the most untapped source of advancement is the integration of optogenetics with other technologies. These include methods to determine global wiring, volumetric, genetically targeted methods to visualize and control activity within intact tissue, and non-optical methods with a recoverable trace to sidestep light scatter (Figure 10).[190] Using both established and novel techniques in tandem will provide a path to achieve fundamental goals en route to mapping the neuronal circuitry of the brain.

4.2. Nanomaterials for Molecular/Ion Sensing, Monitoring and Stimulation

Ion channels are naturally engineered pore-forming proteins that act as a bridge between the internal and external environments of a cell. Throughout the body, more than 300 different types of these ion channels are integrated with cell membranes.[191] These channels are integrated with various physiological functions including, but not limited to, formation of resting membrane potential, synaptogenesis and regulation of cell volume. Additionally, ion channels are critical to cells' ability to receive, process and transmit signals, which are essential cellular processes. A unique and integral aspect of these channels is their ability to activate themselves in response to ligands, such as neurotransmitters, or changes in voltage.

Furthermore, action potentials, which are the basic elements of information signaling in the brain, rely on the proper function of ion channels. Neurological diseases can potentially be products of the absence or mutations of these important proteins.[192] Excess activation of these channels may also lead to various neurological diseases, including stroke, AIDS dementia complex, amyotrophic lateral sclerosis, and Alzheimer's disease. Thanks to the combination of molecular-based technology and electrophysiology, research in the past 30 years has led to the exploration of diseases caused by the mutation of genes expressing ligand- and voltage-gated ion channels, known as channelopathies.[193] Research on these channelopathies has been utilized for non-monogenic aetiology, the understanding of various hereditary disorders and the understanding of disease-causing gene mutations.[193,194]

The combination of molecular biology, nanotechnology, and electrophysiology has led to great progress in understanding ion channels within the nervous system because of the ability to monitor the flow of ions within a neuronal circuit. The study of the flow of ions within neuronal circuits has gained the attention of neuroscience researchers because of the various signaling components present in the nervous system that rely on ion movement.[195]

Recently, the development of nanoscale sensors and electrodes has allowed researchers to monitor the flow of ions within the neuronal circuit of the brain based on the high sensitivity, wide potential window, and biocompatibility of these products.[196]

One study showed that carbon nanofiber-based wireless instantaneous neurotransmitter concentration systems (WINCS) have greater selectivity and sensitivity in detecting neurotransmitters than macroelectrodes. These WINCS detected the individual concentrations of neurotransmitters in a mixture of dopamine (DA), serotonin (5-HT), and ascorbic acid at concentrations as low as 50 nM for DA and 100 nM for 5-HT by utilizing differential pulse voltammetry.[48]

Additionally, neurotransmitter sensors have been developed. For example, one group developed a wireless carbon nanofiber-based neurotransmitter concentration sensor utilizing fast scan voltammetry (FSCV) in vitro to simultaneously detect dissolved oxygen and dopamine.[47] These results show promise for the utilization of carbon nanofiber electrodes and the application of time-independent decoupled waveforms to detect multiple neurotransmitters. Thus, there is potential for CNF electrodes to aid the elucidation of the mechanism of deep brain stimulation and, consequently, provide an improved understanding of the pathophysiology of nervous system disorders.

Fluorescence imaging is a widely used technique in the study of neuroscience due to its ability to study detailed morphological structures and measure intracellular physiological processes.[197] As mentioned previously, there is a lot of potential and desire to accurately measure and observe ion flows within the nervous system. Utilizing fluorescence imaging to study the flux of ions within the nervous system is a promising application, but difficulties in measuring many ions, such as Cl^-, Na^+, and K^+, remain. Within the nervous system, sodium flow and the transmembrane sodium gradient are important for the proper function of many vital physiological functions, but currently available Na^+ probes have poor qualities that hinder the accurate measurement of Na^+ flow during these functions.[198] Studies investigating the utilization of fluorescence imaging to measure ions such as Na^+ have been limited by the cell sizes used.[199] One recent study examined a method in which the intracellular half-life of a Na^+ dye, such as CG, was prolonged by encapsulating it in a dendrimer.[200] The same group also investigated the idea of utilizing this principle for a Na^+ nanoprobe to probe physiological processes in thick tissue preparations. The observations during this investigation generated promising results by showing that this system could sense Na^+ in cells and tissues at even lower concentrations. This idea of a nanosensor to measure ion flow holds promise in the field of neuroscience because of the many neuronal processes that require ions, such as Na^+.[201]

Utilizing optical sensors is another promising method to visualize ion flow in the nervous system. Optical sensors work by translating the measured physical quantity of light into an electrical signal that can be read by the instrument. Scientific collaborations have produced optical sensors that can measure the voltage of ion channels, which have the potential to allow visualization of both the electrical dynamic and complex interactions among neurons.[202] In more recent years, there has been development of a variety of genetically encoded fluorescent voltage sensors with the ability to detect collective neural activity in vivo and single spikes in vitro.[203]

The unique properties of QDs allow them to be optimized for voltage sensing and for light-controlled electrical activation of cells. Recent studies have also indicated potential for ultra-bright QDs to aid the detection of action potentials in the nervous system.[204] Recently, one group investigated and quantified the voltage-dependent photo-physical properties of QDs to assess the effectiveness of this method.[205] In the study, the group investigated and modelled different parameters in the use of QDs for voltage imaging, such as the QDs' optical properties, neurophysiological parameters, and optical instrumentation settings. Subsequent calculations determined the effectiveness of the QDs in both wide-field epi-fluorescence and laser-scanning microscopy to detect spikes in action potentials. The study ultimately concluded that the properties of QDs, including their brightness and voltage sensitivity, should allow the detection of many cells simultaneously.[185]

Another group showed that ion channels in cells can actually be controlled by magnetically heating NPs.[206] NPs that were sensitive to radio waves and thus became heated upon exposure were used to activate temperature-sensitive ion channels in cells (Figure 11). During the study, superparamagnetic ferrite NPs were used to target specific membrane proteins that express the temperature-sensitive transient receptor potential V1 (TRPV1). Upon exposure to the radiofrequency, the superparamagnetic ferrite NPs generated sufficient

heat to open and close the ion channels in cultured cells and thus generate action potentials. The temperature increases in this method were highly localized within the cells, as detected using fluorophores.[132]

When the same group applied this approach in a living worm, they obtained very interesting results. In response to the localized temperature increase, the worm moved in the backwards direction (Figure 11D). The control worms in the experiment did not exhibit such responses. The controlled opening and closing of the channels in the worms by NP heating caused behavioral responses, which may be of interest in the study of neuronal signaling. The neuroscience community can expand upon these results to study and hopefully better understand how behavioral responses are generated from the opening and closing of protein ions channels within the nervous system. In future years, this technology could potentially be studied in more complex neuronal models, such as the mouse or human brain.[206]

4.3. The Piezoelectric Effect: Novel Nanomaterials for Neuroscience Applications

Hebb's Law underpins much of our understanding of both the development and functional recovery of neuronal networks. It is not sufficient for tissues to simply develop the appropriate cytoarchitecture, as differential electrical activity is a fundamental drive that permits them to evolve into the sophisticated functional networks that we seek to measure, imitate and restore. One might postulate that piezoelectric materials, with their capacity for deformation-dependent mechanical-electrical transduction, may represent promising structures upon which nanoengineering and neural regeneration-based medical interventions can be built.

Investigations based on this rationale have already begun to bear fruit. It has long been known that the application of an external electrical stimulus can enhance neurite outgrowth on the surface of conductive substrates, including poly(D,L-lactide-co-epsilon-caprolactone) (PDLLA/CL) and polypyrrole (PPy).[207] However, the logistical challenges associated with the use of an external electrical supply renders this approach less than ideal. In theory, utilizing piezoelectric materials presents a solution to this problem. By relying on internal mechanical deformations to produce a transient electrical response, rather than an external current, an electrical connection to an external voltage source may no longer be necessary to optimize neuronal regrowth. Piezoelectric materials have been shown to enhance neural regeneration in animal models of spinal cord and cortical neuron lesions, with conductive polymers proving to be highly permissive for axon growth and myelination in vitro.[208] These successes with non-nanomaterials have provided a basis for further investigations using nanomaterials. Translating these proof-of-concept experiments directly to neuronal tissue nanoengineering strategies has taken more time, but the results have been promising.

Recently, Guo et al. introduced a new and promising strategy for combining a low-cost, small, and long-lasting human-motion-driven triboelectric nanogenerator (TENG) with electroconductivity-improved reduced graphene oxide-poly(3,4-ethylenedioxythiophene) (rGO-PEDOT) hybrid micro-fibers to build a self-powered electrical stimulation system for neural differentiation (Figure 12).[209] As the power source, the human-motion-driven TENG generated an output of 300 V and 30 μA. The rGO-PEDOT hybrid microfibers, which acted as the scaffold, induced MSC differentiation into neural cells with neural-

specific proteins and gene expression greater than those of rGO microfibers, the control. The hybrid microfibers had good mechanical strength, cytocompatibility and biodegradability properties. This study showed that nanomaterials with piezoelectric properties are indeed a viable strategy for neural regeneration.[209]

Expanding on these initial experiments, the functionalization of nanomaterials with piezoelectric properties has already started in earnest, with tentative steps underlying exciting prospects for the next generation of biomaterials for tissue regeneration. One route involves the incorporation of an electrical stimulus or signalling molecule onto a nanomaterial scaffold with piezoelectric properties. Ceramics such as zinc oxide and silicon dioxide are somewhat atypical candidates for neuroscience applications, but their excellent piezoelectric properties as well as capacity for fabrication into a vast array of nanostructures make them popular in this circumstance.[210] First-principles investigations have examined combining ZnO with a polymer to form a nanorough surface with a flexible tubular shape. This creates a free boundary within the structure that permits the atoms within to assume a wider stoichiometric array of positions, thereby enhancing the dynamics of the piezoelectric effect.[211] These experiments, though in their relative infancy, give a taste of a potential future for nanotechnology in neuroscience based on the piezoelectric effect.

5. Neurotoxicity of Nanomaterials (Nanoneurotoxicity)

By engineering particles on the scale of molecular-level entities–proteins, lipid bilayers and nucleic acids–we can stereotactically interface with many of the components of cell systems, and at the cutting edge of this technology, we can begin to devise ways in which we can manipulate these components to our own ends.[212] However, interfering with the internal environment of cells, especially neurons, is by no means simple. Further, by invading the permeability barrier represented by the cell membrane, we open doors not only to opportunity but also to toxicity. Part of the difficulty in assessing nanotoxicology is the complexity and scale of toxic events. These events do not operate solely on an isometric biochemical or structural format amenable to simple in vitro tissue studies. Instead, they interact heavily with components and pathways in both the biochemical environment of the cell and physiological system.[213,214] The result is a multi-layered dynamic process with an indelible temporal dimension, with potential sources of damage in homeostatic disruption, bioaccumulation and free radical release.

Metal oxide NPs, for example, are highly utilized in fields such as medicine and engineering for their large surface area to volume ratios. However, these NPs have high chemical reactivity and toxicity as a consequence of their small size and large surface area. More specifically, there is concern about the negative health effects of metal oxide NPs on the nervous systems of living creatures. These NPs can accumulate in structures of the brain, such as the cerebellum and cortex. Additionally, metal oxide NP deposition may lead to oxidative stress, pathological changes, and inflammatory responses.[215] Despite these possible observed consequences, there are very few federal or state regulations on the manufacture, use, transportation, sale or disposal of such nanomaterials.[216]

Additionally, the synthetic diversity and extraordinary thermomechanical properties of CNTs make them well-suited for a multitude of electrical and structural applications, including tissue engineering.[217] However, studies such as those by Zhu et al. have inferred a significant degree of genotoxicity (DNA interference) in the use of MWCNTs as scaffolds, [218] symptomatic of a wider challenge presented by the use of nanomaterials. In addition, several metal NPs, including titanium oxide, zinc oxide, magnesium oxide, silver, iron oxide (Feo, Fe_2O_3, Fe_3O_4), copper, copper oxide, aluminium oxide, (alumina, Al_2O_3) and silicon oxide, highly interact with the cellular environment and cause serious health risks to neurons and brain function.[215,219]

Hence, nanotoxicology profiling is a critical component of studies of nanomaterials. The factors that must be considered in nanotoxicology studies are shown in Figure 13A. Among these factors, understanding the chemical and physical properties of nanomaterials is a vital element in understanding their neurotoxic effects. Studies requiring the use of nanomaterials should include thorough physiochemical studies at all steps of their use in biological systems. In biological systems, there are possibilities of differing accumulation and distribution of nanomaterials to target organs, as well as across the BBB, as a consequence of differences in nanomaterial qualities such as size, shape, agglomeration, aggregation, purity, solubility, stability, dispersant, surface coating, surface reactivity, range of dose and dose rate/response (analysis of dose relationship, for in vitro and in vivo extrapolation).[220] In nanotoxicology, the hazards of various nanomaterials must be tested alongside the evaluation of their physiochemical properties as mentioned above, and risk assessment and management studies must continue to gather data to obtain a comprehensive understanding of toxicity exposure during the life cycle of NPs (Figure 13B).

If we are to continue to make great strides in nanoneuroscience, functional investigations of nanomaterials must be complemented with robust toxicology studies. A database on the toxicity of materials that fully incorporates these findings for use in future schema must be developed (Figure 13C). These databases should include information and data on i) the chemical nature of the nanomaterials in complex aqueous environments, ii) the biological interactions of nanomaterials with chemical specificity, iii) the effects of various nanomaterial properties on living systems and iv) a model for the simulation and computation of possible effects of nanomaterials in living systems across varying time and space.[213,214] If we can establish such methods, it may be possible to design nanopharmaceuticals for improved research as well as quality of life.

6. Summary, Challenges and Future Perspectives

Nanoneuroscience integrates what is known about the nervous system and nanotechnology, two swiftly progressing fields. The marriage of these two disciplines may provide a solution to many CNS disorders, from neurodevelopmental disorders to psychiatric disorders and motor and sensory disorders. The horizon is far and wide, but through organized contemplation of what is currently available, it is possible to systematically approach nanoneuroscience. Studies of the properties and functions of nanomaterials will be the mainstay of nanoneuroscience, which forms the basis of neuroscience applications such as drug delivery, neuroprotection, neural regeneration, neuroimaging and neurosurgery. The

story does not end there as nanotechnology is invading other fields, including optogenetics and the piezoelectric effect, which hold further hope for curing CNS disorders.

However, challenges in nanoneuroscience are present in many forms, such as neurotoxicity; the inability to cross the BBB; the need for greater specificity, bioavailability and short half-lives; and monitoring of disease treatment. The nanoneurotoxicity surrounding these nanomaterials is a barrier that must be overcome for the translation of these applications from bench-to-bedside. While the challenges associated with nanoneuroscience seem unending, they represent opportunities for future work.

Sustained research progress in nanoneuroscience, an emerging new area, with the aid of nanoscience has yielded significant improvements in our understanding of the operation of biological systems, the functions of different parts of the brain and the pathophysiology of disease in the nervous system. However, a comprehensive understanding of neurons and their functional circuits in the brain remains elusive. Still, it could be argued that mankind's understanding of how the brain works, how neurons transform signals into outputs and how neurons communicate to control the complex environment, i.e., the body, is one of the greatest remaining challenges (Table 4).

Future investment in these areas will create ever more sophisticated, increasingly functional and safer platforms for the pursuit of both scientific and clinical endeavours. In parallel, continuing progress is needed in characterizing the fundamental molecular, physiological and pathological features of the nervous system. The greater our basic knowledge of neuronal networks, the stronger the foundation upon which nanotechnology can successfully be applied. Special attention is needed to investment in the generation of safe and sustainable nanomaterials. Ultimately, if these fields are studied in tandem and measures are implemented to meet such challenges, it is only a matter of time before nanotechnology-based interventions for nervous system disorders reach the clinic.

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Biographies

Anil Kumar received his PhD (2013) in nanoscience from the National Center for Nanoscience and Technology (Chinese Academy of Sciences, CAS), Beijing, China. He

worked with Prof. Hong Liu as a postdoctoral scientist at the Beijing Institute of Nanoenergy and Nanosystems, Chinese Academy of Sciences, Beijing, China. He is currently a postdoctoral research associate in the Department of Chemistry at the University of Georgia in Athens, GA USA. His main research interests include nanomedicine for neuroscience and cardiovascular disease and nanotechnology to circumvent drug resistance in cancer.

Dr. Aaron Tan is an MBBS-PhD medical student in his penultimate clinical year at University College London (UCL) in the UK. He graduated with an upper second class honours (2:1) BSc in Surgical Sciences at UCL in 2011, and a PhD in Surgery and Bioengineering at UCL in 2014. Aaron's research interests are in nanotechnology for medical and surgical applications.

Hong Liu is a professor in State Key Laboratory of Crystal Materials, Shandong University, and an adjunct professor in Beijing Institute of Nanoenergy and Nanosystem, Chinese Academy of Science. He received his PhD degree in 2001 from Shandong University (China). His current research is focused mainly on tissue engineering, nanomaterials and nanodevices (neuron cells response and recording), especially the interaction between stem cell and nanostrucuture of biomaterials.

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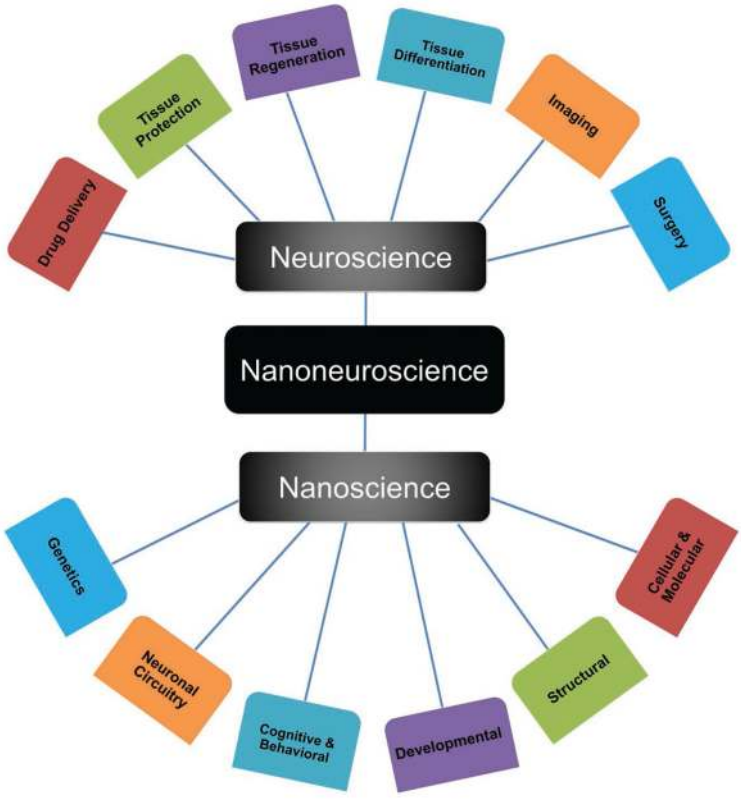

Figure 1.

Schematic illustration of the relationship between nanotechnology and neuroscience. The two fields are closely intertwined, and it is difficult to clearly separate any one subfield. A new field (nanoneuroscience) is emerging with the combination of two different sciences to gain a better understanding of brain function.

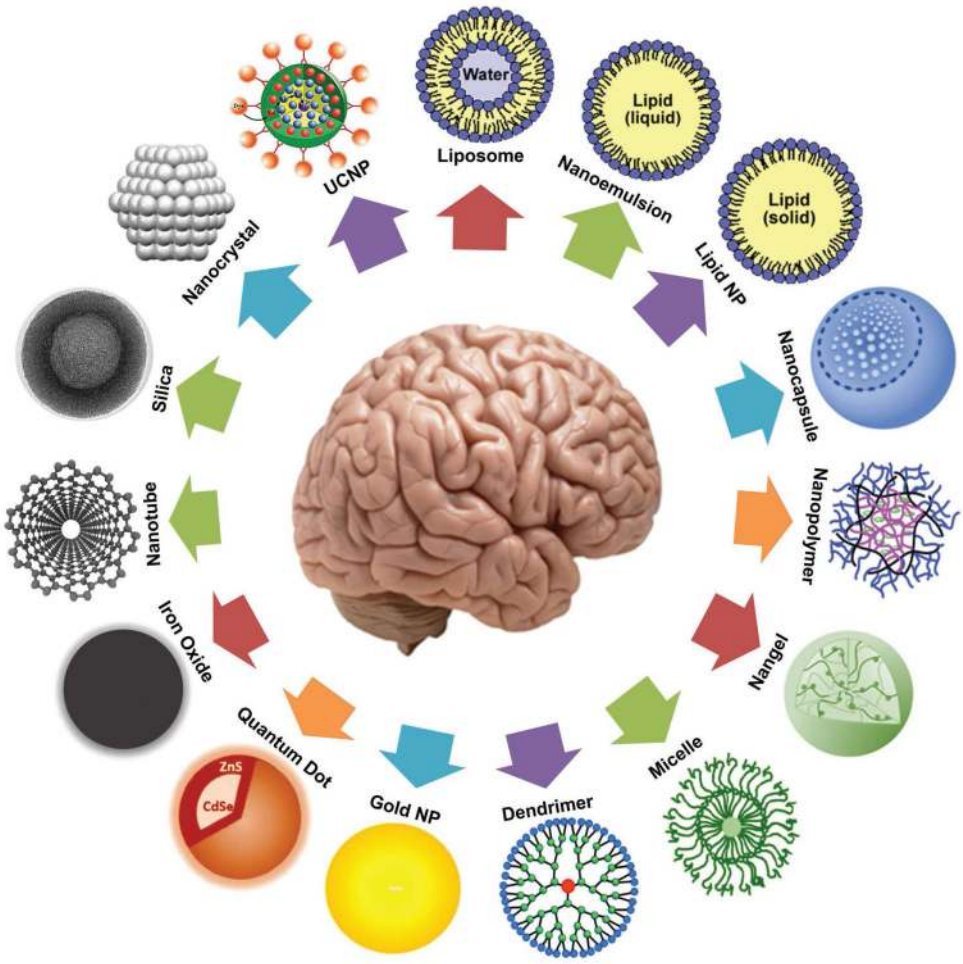

Figure 2.

Schematic representation of different types of nanoparticle-based platforms and their roles in neuroscience applications. These nanoparticles (NPs) have been extensively used in neuroscience to investigate their potential applications for the diagnosis, treatment and monitoring of several neurological diseases. Some of the polymer NP images were adapted from Gu et al. with modification. Reproduced with permission.[15] Copyright 2011, RSC Publishing. UCNP figure credit: Reproduced with permission.[221] Copyright 2015, ACS Publisihing. Nanocrystal figure credit: Reproduced with permission.[222] Copyright 2012, PNAS Publishing. Silica figure credit: reproduced with permission.[227] Copyright, AMES Laboratory/US Dept of Energy. Nanogel figure credit: reproduced with permission.[223] Copyright 2010, Taylor and Francis Publishing Group. Liposome, nanoemulsion, micelle, lipid NP figure credit: reproduced with permission.[224] Copyright 2014, InTech. Nanocapsule figure credit: Reproduced with permission.[225] Copyright 2015, SCIELO Publishing. Dendrimer figure credit: Reproduced with permission.[226] Copyright 2014 RSC Publishing.

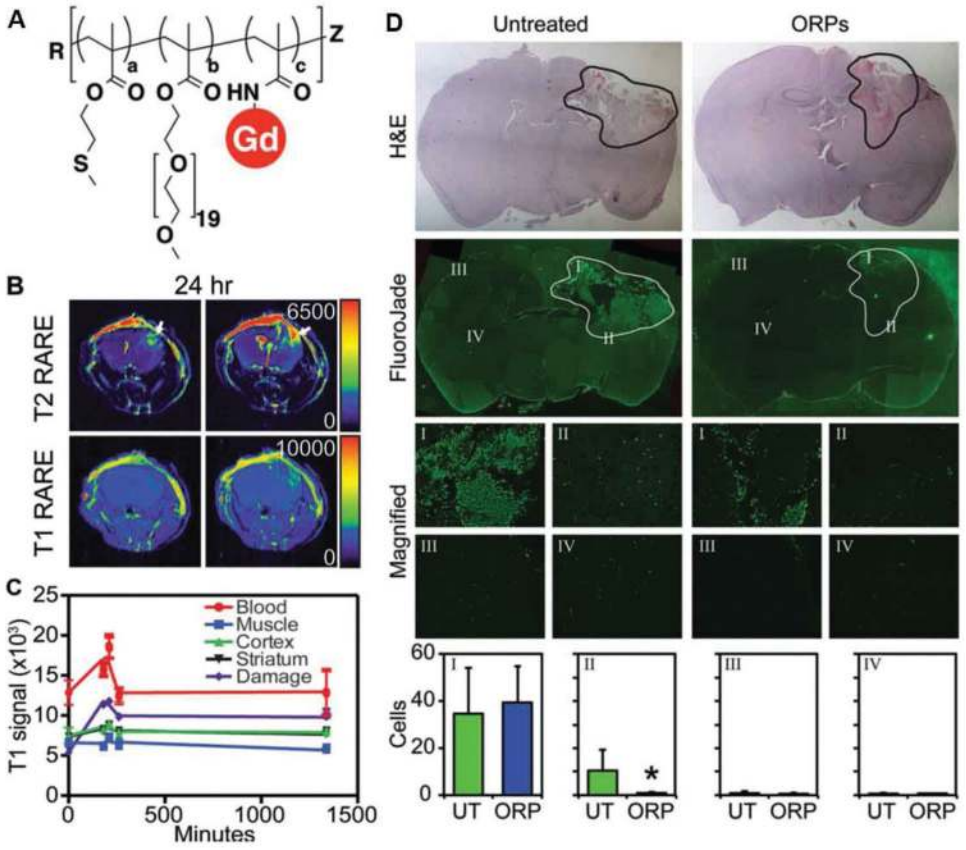

Figure 3.

ORP and its therapeutic evaluation in a mouse model of TBI. **A**) Schematic representation of ORP synthesis and chemical structure. **B**) T2 RARE (TE = 90 ms, TR = 3000 ms) images show the oedema caused by TBI and provide an indication of the extent of damage (white arrows). High signal intensity regions depicting OPR accumulation can be seen in the T1 RARE images and correlate with the damaged regions depicted in the T2 RARE images. **C**) T1 signal intensity quantification from a single animal, revealing uptake and retention of ORP in damaged areas of the brain but absence in other areas. **D**) FluorJade C staining showing evidence of reduction of neurodegeneration in the initial and surrounding injury site after 24 hours in mice treated with ORP. A count of damaged neurons was manually performed in each of the following regions: I) the CCI site, II) the deep margin of the CCI site subject to secondary damage, III) the contralateral cortex, and IV) the contralateral striatum. Untreated is indicated by UT. Reproduced with permission.[102] Copyright 2016, Wiley-VCH.

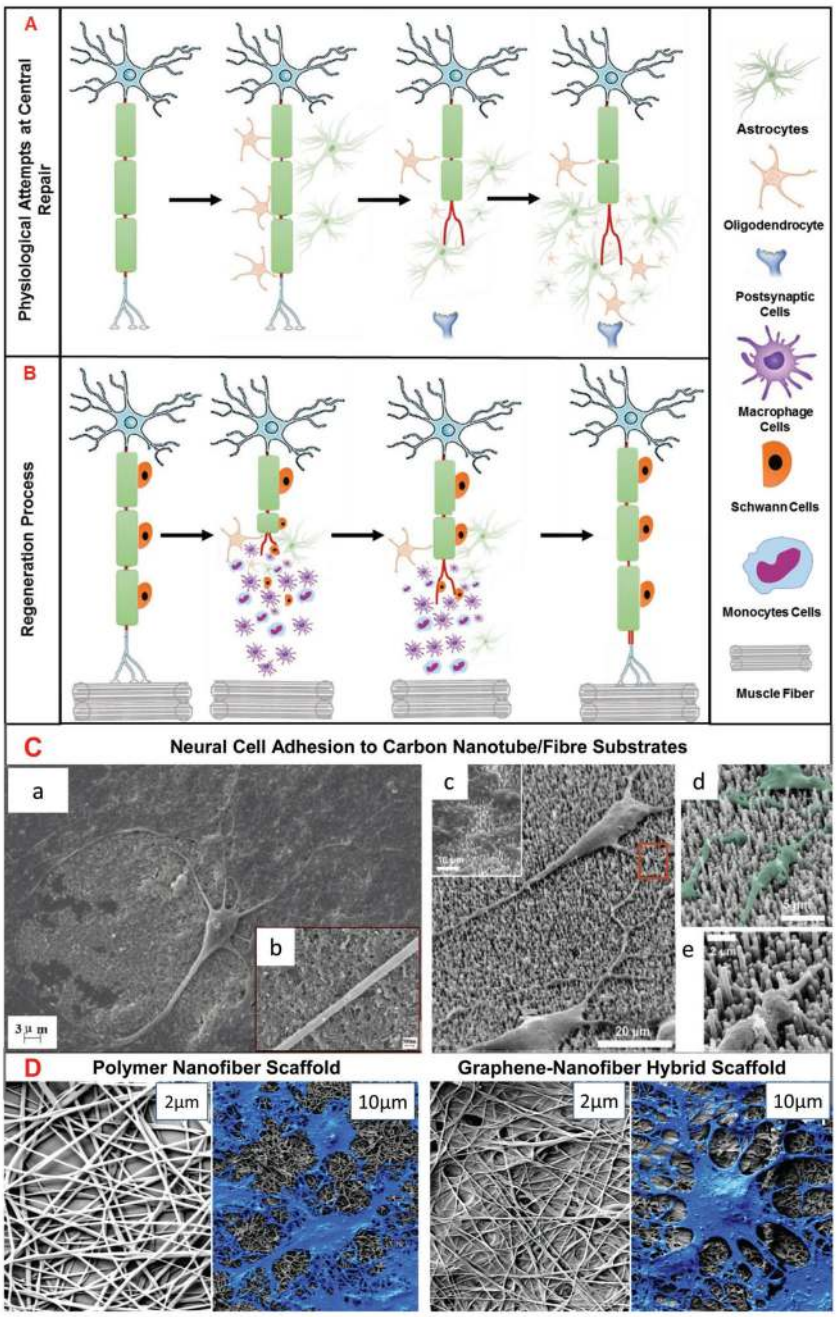

Figure 4.

Schematic illustrating injured nerve regeneration in the central and peripheral nervous systems. **A)** Physiological attempts at central repair result in glial scar tissue formation due to the combination of inhibitory glial factors and a general non-permissive environment. **B)** The peripheral recovery process entails regeneration involving the activity of Schwann cells, macrophages and monocytes. **C)** Scanning electron micrograph images demonstrating neural cell adhesion to carbon nanotube/fiber substrates, which act as a scaffold similar to muscle fiber as predicted in Figures A&B above. (a) Neonatal hippocampal neurons adherent to MWCNT glass substrates, with extended neurites by 8 days. (b) Inset image showing a

single neurite in close contact with carbon nanotubes. Reproduced with permission.[124] Copyright 2015, American Chemical Society. (c, d, e) PC-12 neural cells grown free-standing on vertically aligned CNFs coated with polypyrrole at various magnifications. Reproduced with permission.[126] Copyright 2008, Elsevier. **D)** Graphene-coated on a polymeric nanofiber hybrid scaffold promotes the selective differentiation of neural stem cells into oligodendrocytes. Reproduced with permission.[127] Copyright 2014, Wiley-VCH.

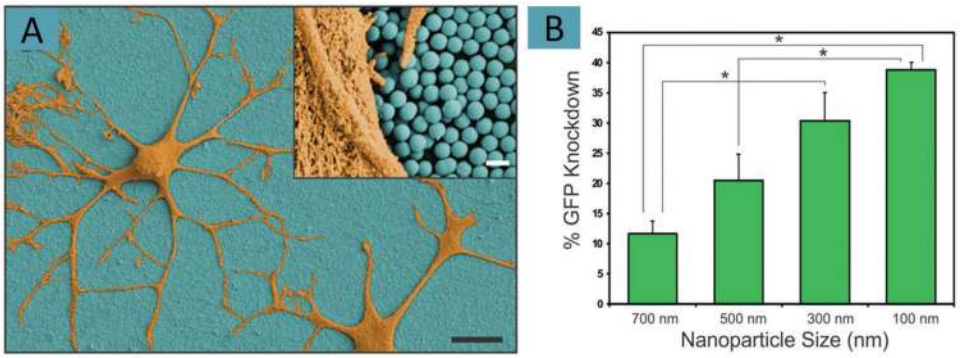

Figure 5.

A) A scanning electron microscope (SEM) image of the NanoRU system with NSCs growing on top **B)** Quantitative graph showing the dependence of GFP (green fluorescence protein) knockdown on silica NP size in the NanoRU system. Reproduced with permission. by Nature Publishing Group Ref. [133]. Copyright 2013, Nature Publishing Group.

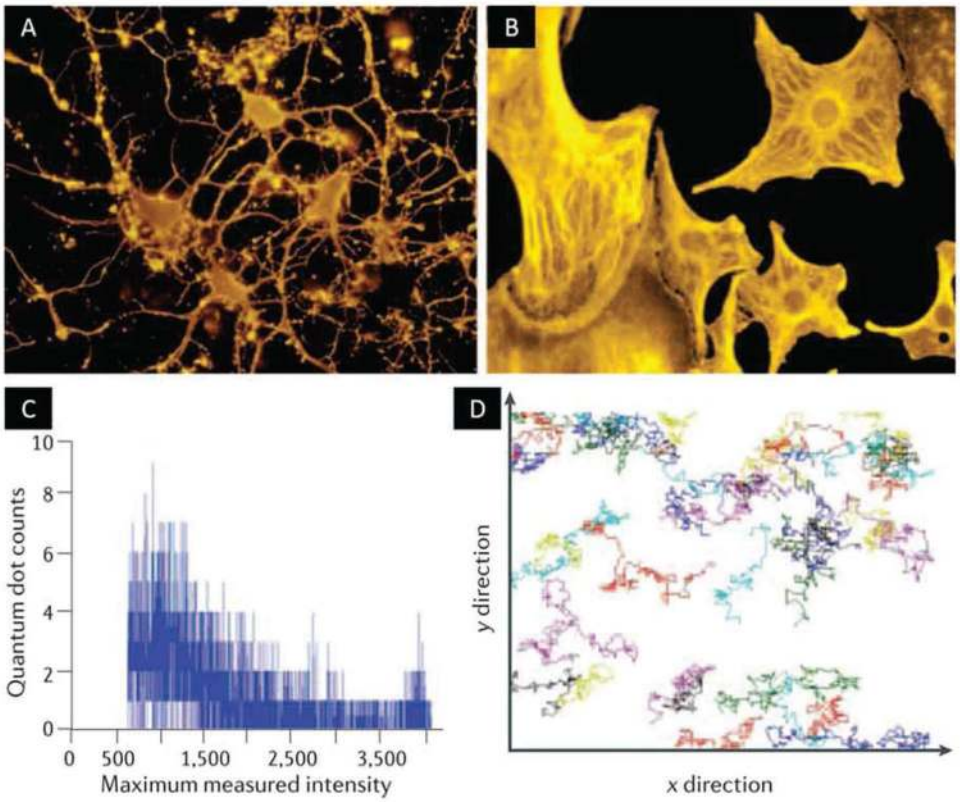

Figure 6.

Quantum dot (QD)-labelling with B-nerve growth factor (BNGF): **A)** Primary rat cortical neurons labelled with QD-anti-β-tubulin III antibody conjugates. β-tubulin is a neuron-specific intermediate filament protein and thus an effective neuronal marker. **B)** Primary rat astrocytes labelled with QD-anti-glial fibrillary acid protein (GFAP) antibody conjugates. GFAP is a glial-specific intermediate filament protein. **C)** QD nanotechnology offers the advantage of providing both quantitative and qualitative datasets. Individual QDs can be counted across a sample image to generate information pertaining to the distribution and number of ligand-target receptor interactions. This particular graph illustrates the number of QDs with a given intensity. **D)** QDs can be functionalized for single-particle tracking of ligand-target pairs – such as the motion of a receptor within a lipid bilayer. This diagram illustrates the trajectory of a field of 55 QDs undergoing Brownian diffusion. Reproduced with permission.[3] Copyright 2006, Nature Publishing Group.

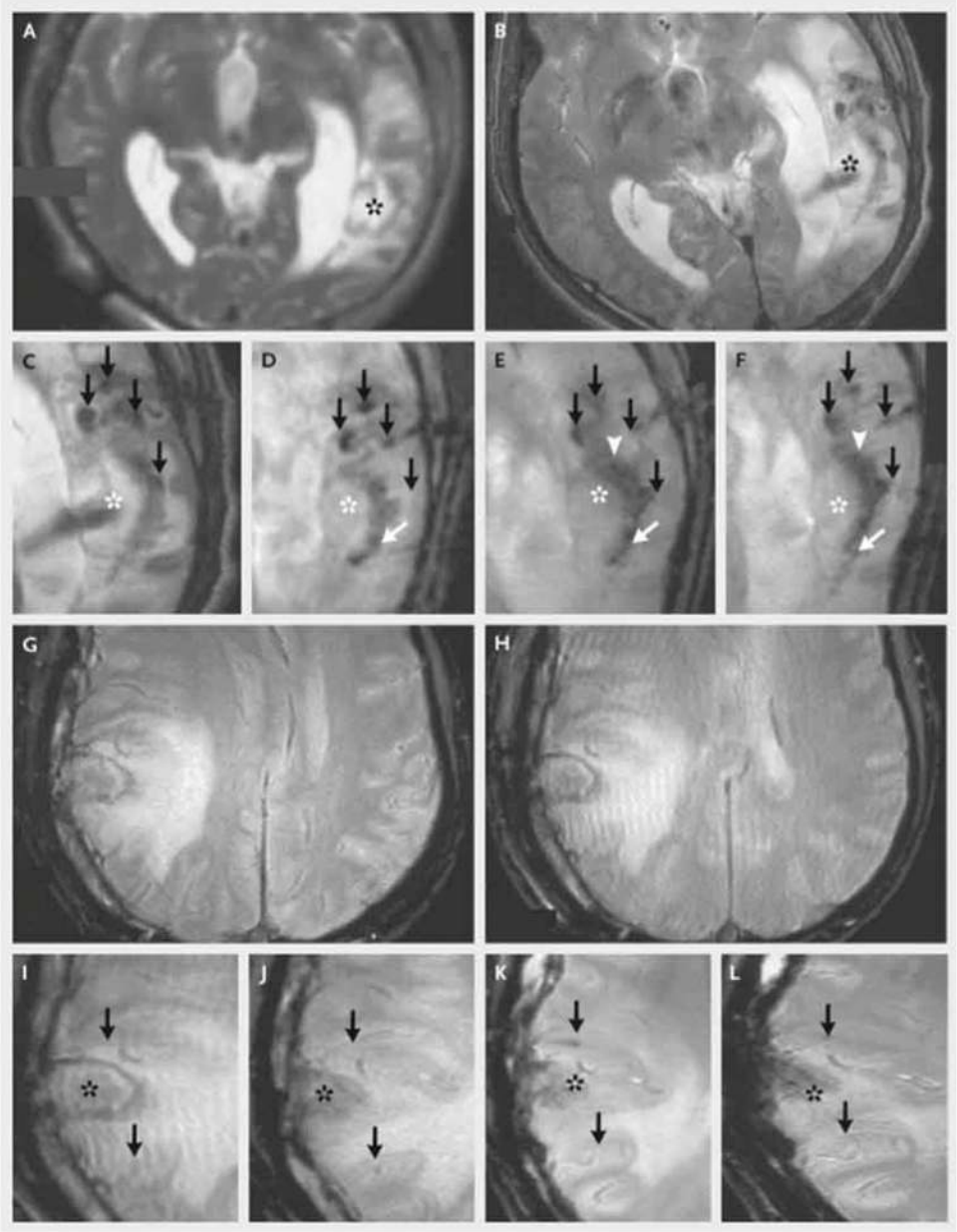

Figure 7.

MRI scans from a patient receiving iron oxide nanoparticle-labelled neural stem cells. The scan obtained prior to implantation A) showed no pronounced hypointense signal around the lesion in the left temporal lobe (asterisks). One day after implantation, areas of hypointense signals were apparent. (B) Hypointense signals (black arrows) were observed at injection sites around the lesion on days 1, 7, 14 and 21 (C–F). On day 7 (D), dark signals (white arrows) were observed posterior to the lesion, consistent with the presence of the labelled cells. By day 14 (E), the hypointense signals at the injection sites had faded, and another dark signal (white arrowhead) had appeared and spread along the border of the damaged brain tissue. By day 21 (F), the dark signal had expanded and extended further along the lesion (white arrow). The scans in Panels (G) and (H), from a patient who underwent

implantation of unlabelled cells, were obtained on days 0 and 1, respectively, and the magnified views in (I–L) were obtained on days 1, 7, 14, and 21, respectively. A slightly hypointense signal was present around the injection sites in (I–L). In these panels, the black arrows indicate the hypointense signal, and the asterisks indicate the lesion. Reproduced with permission.[147] Copyright 2006, Mass. Med. Soc.

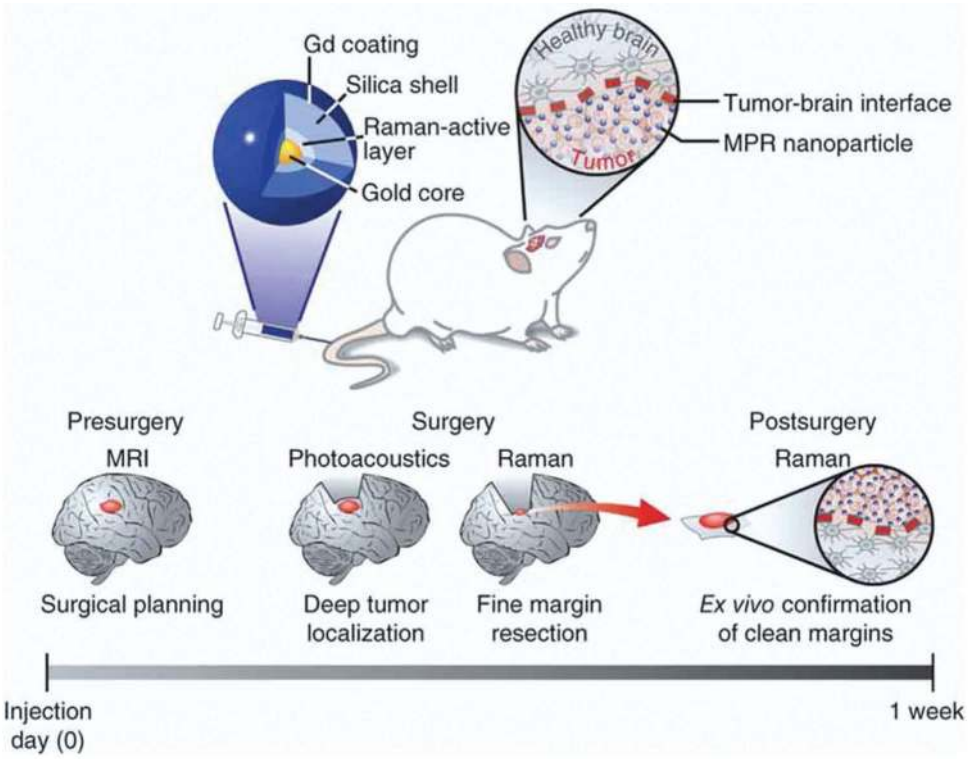

Figure 8.

Schematic representation of the triple-modality MPR concept (MPR stands for magnetic resonance imaging-photoacoustic imaging-Raman imaging). MPRs are injected intravenously into a mouse bearing an orthotopic brain tumor and can cross the BBB and subsequently accumulate in the tumor (above). MRI techniques allow preoperative detection and surgical planning to delineate the tumor. A single dose of the intravenously injected (MPR) probe resulted in efficient accumulation in the tumor and clear detection during the surgical process, even after several days, due to retention. Photoacoustic techniques were used to image the bulk tumor with relatively high resolution during surgery. Raman techniques were used for ultrahigh sensitivity, and spatial resolution was used to remove microscopic residual tumors. Raman probes can be further used to examine the specimen to verify clear tumor margins. Reproduced with permission. Copyright 2012, Nature Publishing Group.[159]

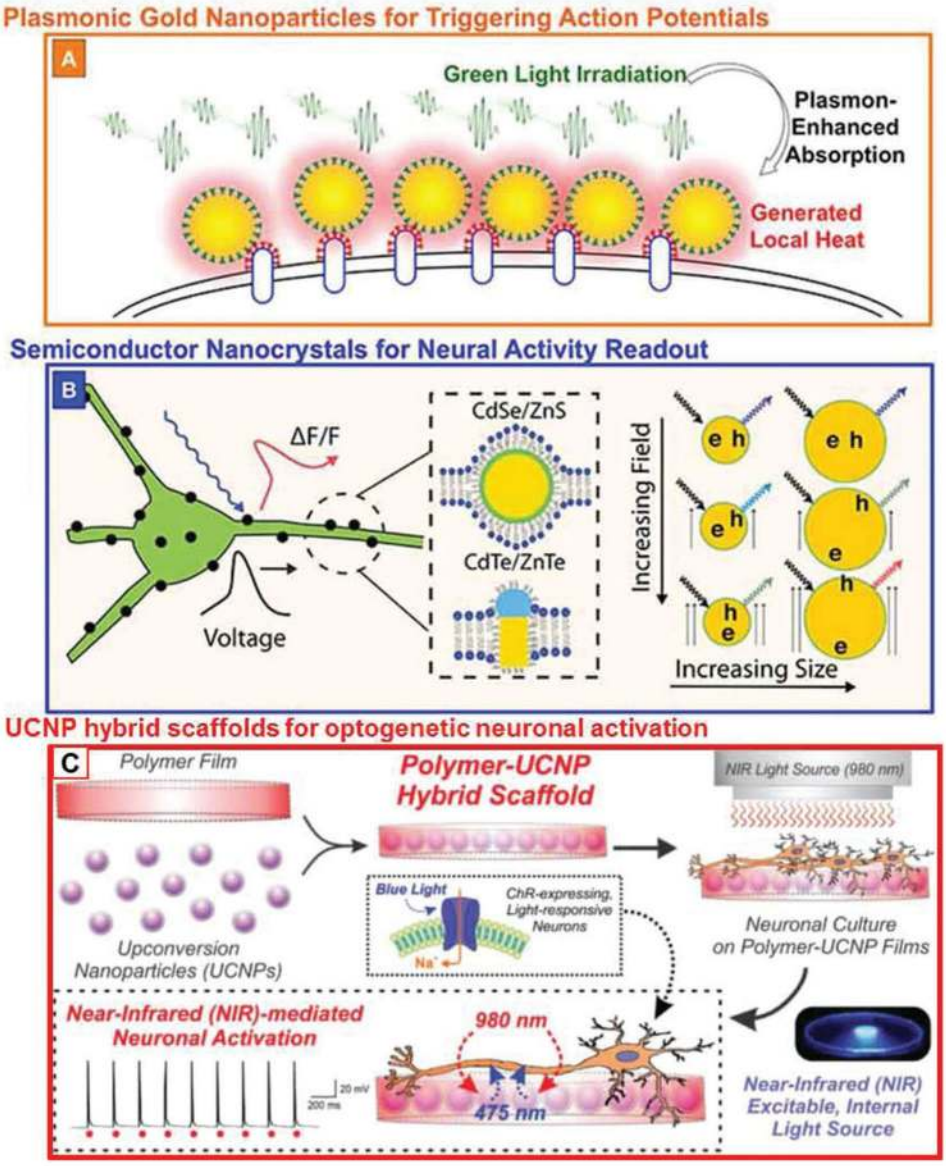

Figure 9.

NPs for optical modulation. **A)** Green light is absorbed by AuNPs, thus generating local heating. Reprocuded with permission.[185] Copyright 2013, Americal Chemical Society. **B)** When the semiconductor nanocrystals are placed near the membrane (lipid bilayer), they sense voltage by detecting fluorescence fluctuations (ΔF/F) generated by the time-dependent electric field. Reprocuded with permission.[182] Copyright 2016, the authors. **C)** Schematic diagram of upconversion nanoparticles (UCNPs) embedded within polymeric films to form biocompatible hybrid scaffolds for neuronal culture. These UCNPs serve as internally excitable light source platform that converts NIR light into blue light, thus facilitating optogenetic activation of channelrhodopsin (ChR)-expressing neurons. Reproduced with permission.[71] Copyright 2015, Royal Society of Chemistry.

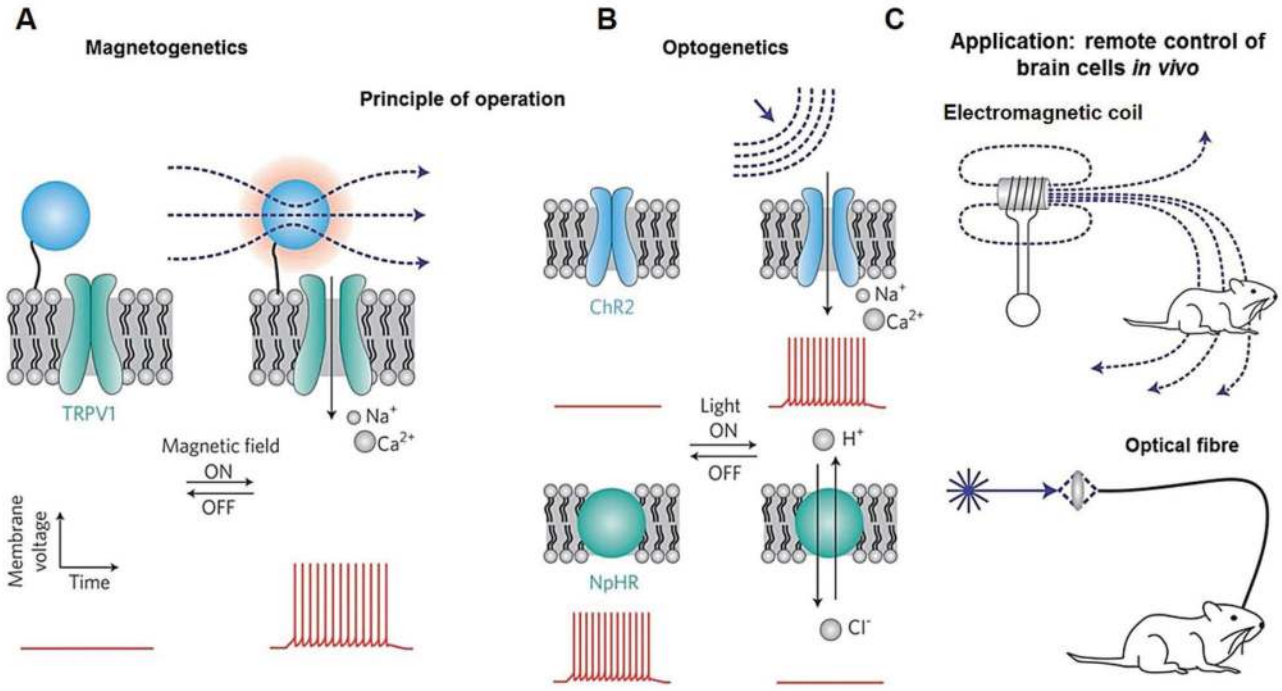

Figure 10.

External control in genetically targeted nerve cells by light (optogenetics) or magnetic fields (magnetogenetics) relies on molecular actuators. These molecular actuators will excite or inhibit the cell when activated by a certain wavelength of light (right) or an altering magnetic field (left). **A)** The magnetic actuators utilize the heating of paramagnetic NPs (blue spheres) when activated by a magnetic field to cause an influx of cations in thermosensitive ion channels (TRPV1). Brain cells can be exposed to an alternating magnetic field through a remote coil. **B)** In the case of optical actuators, the ion channels (e.g., channelrhodopsin-2(ChR2, blue)) or ion pumps (e.g., Np-halorhodopsin (NpHR, green sphere)) are light sensitive. More specifically, these optical actuators are gated by photoabsorption. The membrane-potential traces (red lines) on the right illustrate the generation of light-activated and light-inhibited action potentials by ChR2 and NpHR, respectively. **C)** Implanted optical fibers, for example, may be used as a light delivery method. Reproduced with permission.[190] Copyright 2010, Nature Publishing Group.

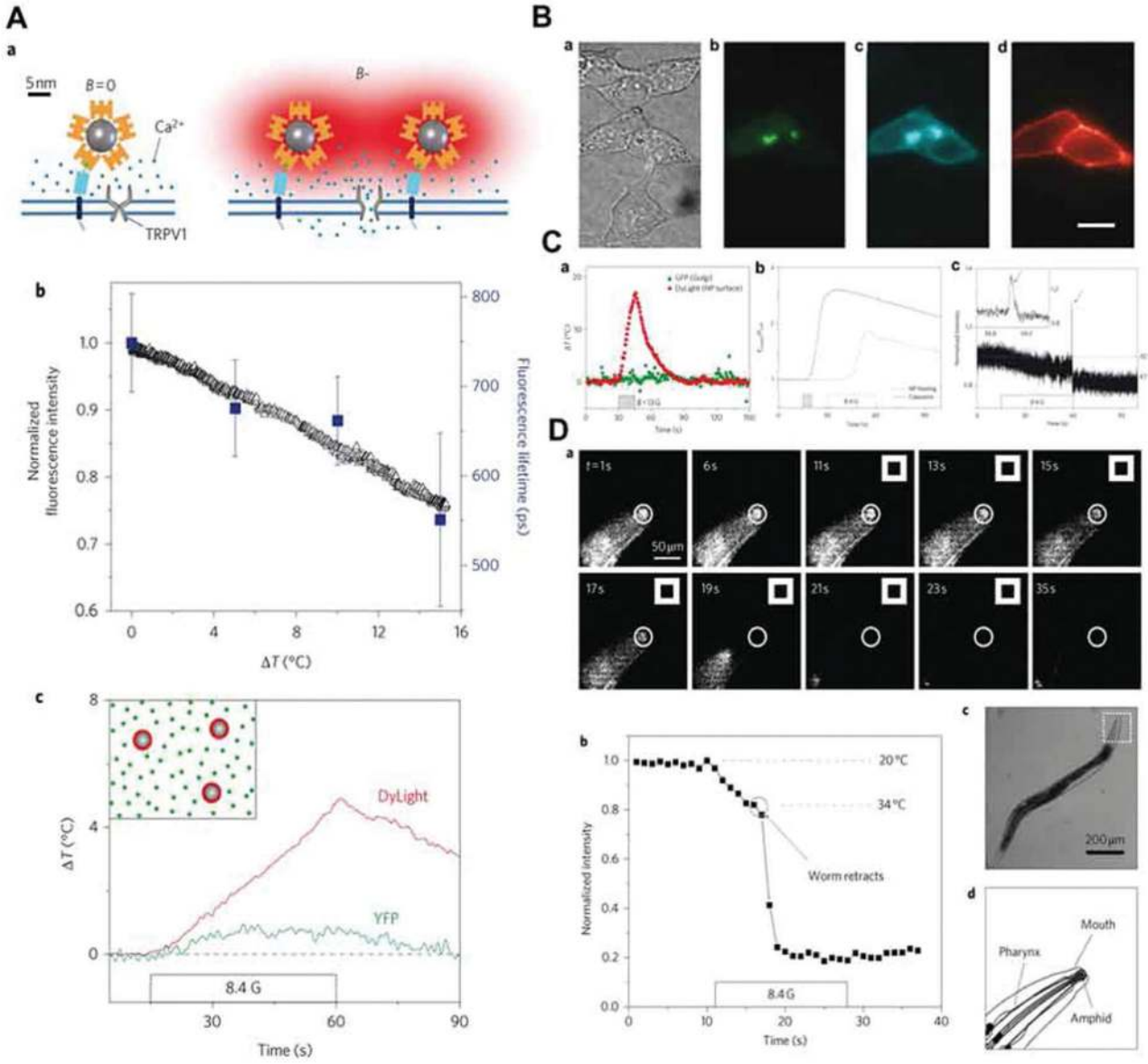

Figure 11.

A) NP heating for ion channel stimulation. a) Heating of superparamagnetic NPs coated in streptavidin-DyLight549 in an RF magnetic field induced the opening of TRPV1 by heat. b) Temperature dependence of the fluorescence intensity and lifetime of streptavidin-DyLight549. c) Graph indicating that applying an RF magnetic field to the NPs induced a change in the surface temperature of the NPs (red line) with little change in solution temperature (green line). **B)** Genetic targeting of NPs to specific cells: a) an image of cells by differential interference contrast (DIC), b) Golgi localized GFP, c) marking of the membrane protein AP-CFP-TM, d) fluorescence of DyLight549. **C)** a) Temperature change in an RF magnetic field of the plasma membrane (red) and Golgi apparatus (green). b) Capsaicin stimulation (solid line) and NP heating (dashed line) effect on TRPV1 opening and calcium influx in HEK 293 cells. c) Induction of action potentials in hippocampal

neurons coated in NPs by an RF magnetic field. **D)** Remote thermal stimulation of *C. elegans.* a) *C. elegans* labelled with fluorescein-PEG-coated NPs, b) fluorescence intensity vs time in the amphid region, c) image of *C. elegans* with head region indicated by the square, d) schematic indicating basic structure of the head region in *C. elegans*. Reproduced with permission.[206] Copyright 2010, Nature Publishing Group.

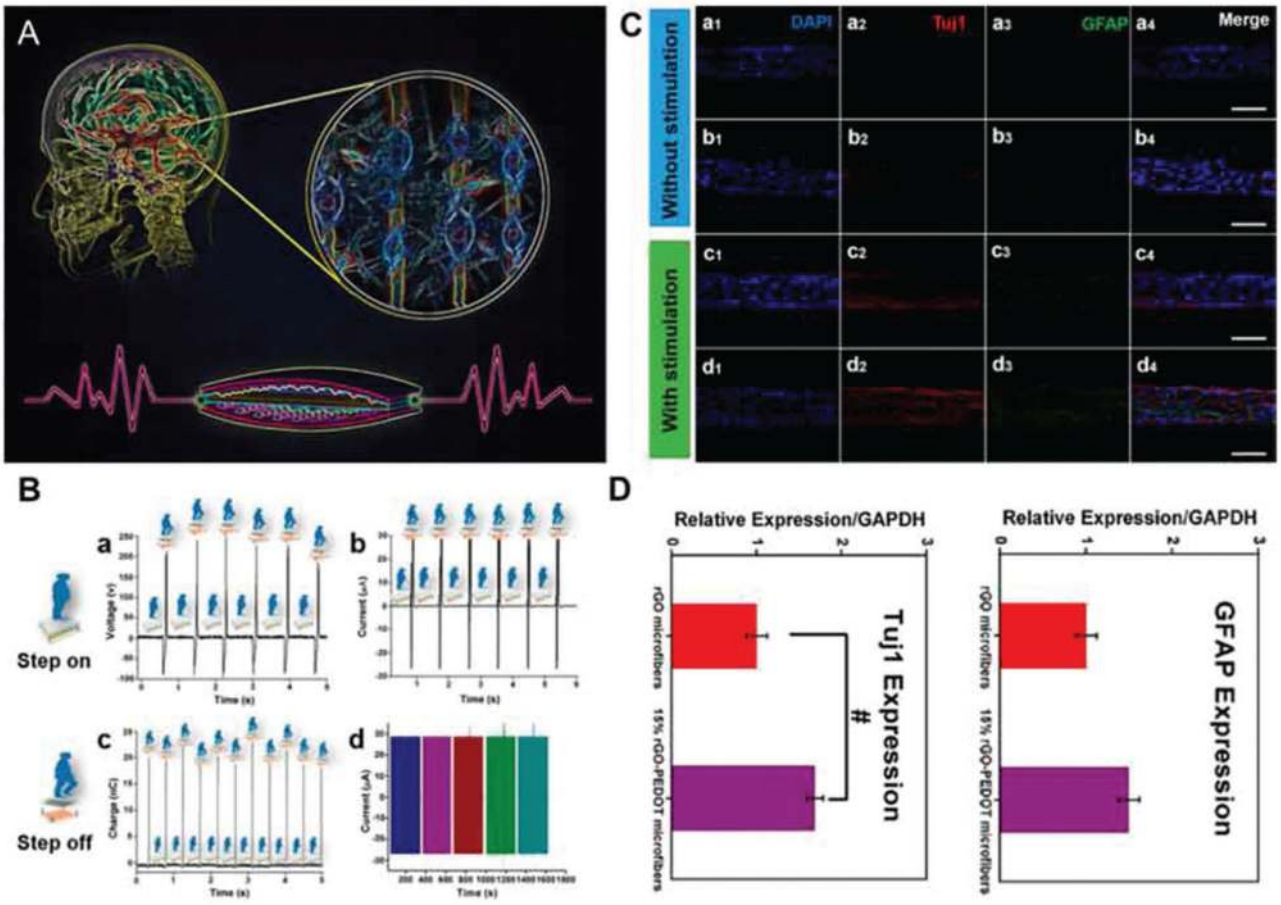

Figure 12.

A) Future application of TENG for neuron differentiation and regeneration in the human brain. **B)** TENG can be operated with human motions, and the typical a) induced voltage, b) current and c) transferred charge of TENG is driven by walking steps. d) Stability of the TENG current output in 1500 s (about 4500 pulses). **C)** Cells were immunostained with (1) DAPI (blue) for the nucleus and neural-specific antibodies (2) Tuj1 (red, cy3), (3) GFAP (green, FITC) after being cultured under stimulation conditions without TENG electrical stimulation (a,b) or with human-motion-driven TENG electrical stimulation (c,d) for 21 days on rGO microfibers (a,c) and 15% rGO–PEDOT hybrid microfibers (b,d). (Right) Merged fluorescence images (scale bar = 100 μm). **D)** Expression levels of neural-specific genes of Tuj1 (a) and GFAP (b) on the rGO microfibers and 15% rGO–PEDOT hybrid microfibers; cells were stimulated by human-walking-driven TENG for 21 days. Reproduced with permission.[209] Copyright 2016, American Chemical Society.

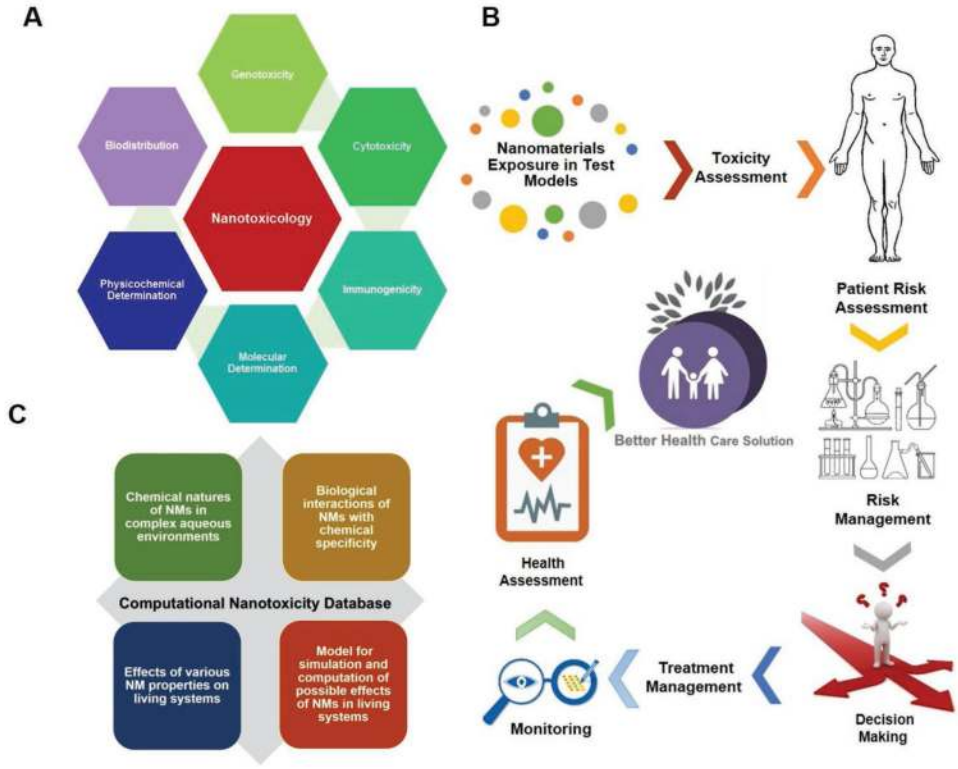

Figure 13.

Considerations in nanotoxicology studies and clinical management. **A)** Typical nanotoxicology studies involve methods to investigate the factors affecting the toxicology of nanomaterials in the application of neuroscience. **B)** Management of nanomaterials for better, health care solutions. **C)** Necessary experimental information required in nanotoxicity databases for efficient use in clinical settings.

Table 1.

Emerging Applications of Nanomaterials in Neuroscience.

Nanocarriers to facilitate intracellular transport
Nanomaterials to initiate cellular and tissue responses
Nanotechnology and varying nanostructures in nervous system disorder studies
Nanomaterials for approaches to the diagnosis and treatment of neurological, neuropsychiatric and neurodevelopmental disorders
Nanodevices and biomolecules for nanoscale exploration of neurons
Using the cytoskeleton as a nanoscale information processor
Modes of neural computation introducing the use of nanowires to explore the mind

Table 2.

Structural and functional properties of nanomaterials and their potential applications in clinical neuroscience.

Nanoparticle Platform		Structural & Functional Properties	Potential Applications in Neuroscience
Organic	Polymeric micelles	• Bilayer vesicles composed of lipids or phospholipids with an aqueous core • Unilamellar or multilamellar • Flexible for synthesis size: 20 to >500 nm, • Easy surface modification and formulation • Rapid cellular internalization and control release • Biocompatibility and low immunogenicity	• Drug delivery to CNS[a)][16] • Neuroprotectionl[17]
	Nanoemulsion	• Oil in water: Oil droplets dispersed in aqueous medium • Water in oil: Water core stabilized by surfactants and co-surfactants • Size: 20 to 200 nm	• CNS, Drug delivery[18] • Neuroprotection[19]
	Lipid NP	• Solid lipid core matrix stabilized by surfactants • Size: 10 to 1000 nm • Easy for conjugation/functionalization • Biocompatibility	• Gene silencing[20] • Neuroprotection[21]
	Nanocapsule	• Solid hydrophobic core with outer phospholipid monolayer • Size: 10to200nm	• Drug delivery to CNS[22] • Neuroprotection[23]
	Nanopolymer	• Solid nanopolymers composed of natural or synthetic biodegradable and biocompatible polymers • Size: 10 to 100 nm	• Scaffold for neuroregeneration[14] • Drug delivery[24] • Neuroprotection[25]
	Nanogel	• Hydrogel composed of cross-linked ionic and non-ionic polymers • Size: <150 nm • Selective surface modification • High degree of porosity and high loading capacity • Controllable/Sustained release	• Drug delivery[26] • Neuroprotection[27,28]]

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Nanoparticle Platform		Structural & Functional Properties	Potential Applications in Neuroscience
	Micelle	• Hydrophobic core stabilized by hydrophilic shell • Size: 10to<150nm • Carriers for contrast agents, imaging[31]	• Drug delivery[29] • Neuroprotection[30]
	Dendrimer	• Spheroid nanostructure consisting of repetitively branched 3D structures • Size depends on number of generations; PAMAM[b)] dendrimer has diameter of 1.5 to 14.5 nm • Very precise size and shape construability • Water solubility and biocompatibility • No elicitation of immune response • Highly electrostatic interaction with nucleic acids	• Drug delivery[32] • Neuroprotection[33]
Inorganic	Gold	• NP[c)] consisting of gold atoms • Low hydrodynamic size: ~2.5 nm • Large available surface area • SPR[d)] and RAMAN[e)] scattering • Easy surface modification and functionalization • Stable and biocompatible	• Nanoimaging and labelling[34] • Drug delivery[35,36]
	Quantum dot	• Colloidal semiconductor crystals with metalloid crystalline core • Can be coated or conjugated with various molecules • Size: 2 to 10 nm • High photo and chemical stability • High molecular excitation coefficient • Potential to permeate with BBB[f)] • Prolonged blood half-life • Minimum adverse effects • Capability to be cleared by phagocytic cells	• Nanoimaging[37–39] and labelling[40]
	Iron oxide	• Magnetite (Fe_3O_4) and maghemite (Fe_2O_3) • Superparamagnetic iron oxide (SPIO) size: 50 to 150 nm • Ultrasmall SPIO size: 10 to 14 nm	• Nanoimaging and labelling[41,42]

Nanoparticle Platform	Structural & Functional Properties	Potential Applications in Neuroscience
	• Large surface area • Small size allows longer circulation and deep tissue penetration	
Carbon nanotube	• Cylindrical nanostructures made of graphene sheets wrapped onto themselves • Size: 1 to 4 nm • Large surface area • High electrochemically accessible surface area (700–1000 m^2 g) • High mechanical strength (elastic modulus ca. 0.64 TPa for an individual nanotube) • Excellent thermal conductivity (individual MWNT[g)] > 3000 W rrr^{-1} K^{-1}), • High electronic current (up to 109 A cm^{-2}) • High penetration efficiency for biological barriers	• Coating to improve electrical inter- face for neuronal stimulation and recording[43,44] • Scaffolds for neuroregeneration[45] • Drug delivery[43] • DNA and protein biosensors[46] • Neurotransmitter sensors[47,48] • Ion channel blockers[49] • Neural tissue engineering[50] • 3D scaffolds for the regeneration of CNS (e.g., brain and spinal cord)[51]
Graphene	• High elastic modulus (ca. 1.0 TPa)[52] • Excellent thermal conductivity (3000 W m^{-1} K^{-1})[53] • High electron mobility (200 000 cm^2 V^{-1} s^{-1}) [54] • Electrical conductivity (1S m^{-1})[53] and low resistivity (ca. 10^{-6} Ω), as a substrate under room temperature conditions[55] • Easy functionalization and good biocompatibility suitable for biomedical applications[56] • Large specific surface area (2630 m^2 g^{-1})[57]	• Materials for neural interfaces[54,58] • Aid in eliciting neurite sprouting[59] • As a 3D niche for neural stem cells (NSCs)[60] • Enhancing neural recording[61,62] • Enhanced signalling in neural networks[63]
Nanocrystal	• Superior optical properties compared to traditional organic fluorescent dyes • Broadband excitation, narrow bandwidth emission • High quantum yield • Resistance to quenching and high photochemical stability[64]	• In vitro and in vivo cytotoxicity analysis[65] • Mitochondrial dysfunction in astrocyte and neuron cells[66]
Silica NPs	• Nonporous or mesoporous (2–50 nm pore size) • Pores allow for enhanced drug loading • Favorable biocompatibility • Highly transparent • Dielectric material (does not absorb light or conduct electrons	• Promotion of nerve cell proliferation and neurite outgrowth[67] • In vivo tracking and imaging[68] • Brain drug delivery[69]

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Nanoparticle Platform	Structural & Functional Properties	Potential Applications in Neuroscience
Upconversion NPs	• Absorb low-energy photons and emit high-energy photons. • Convert long-wavelength near-infrared light (NIR; >800 nm) to short-wavelength visible light (300–700 nm)	• Imaging and cancer therapy[70] • Optogenetic neuronal control[71] • Biosensor for detection of Zn2+ in Alzheimer's disease[72]

a) central nervous system

b) poly(amidoamine)

c) nanoparticle

d) surface plasmon resonance

e) Raman spectroscopy

f) blood brain barrier

g) multi-walled nanotube.

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Table 3.

Nanoparticle-Based Drugs in Clinical Trials and Clinically Approved for Diagnosis and Treatment of Diseases Related to the Nervous System.

Nanoparticle-based Platform		Composition	Trade Name	Therapeutic	Administration	Status	Ref.
Organic	Liposome	Liposome doxorubicin	Sarcodoxome	Soft tissue sarcoma	i.v.[a)]	Phase I/II	[95,96]
		Liposomal vincristine	Onco TCS[b)]	Non-Hodgkin's lymphoma	i.v.	Phase II/III	[95,96]
		Liposomal fentanyl	AeroLEF	Postoperative analgesic	Aerosol	Phase II	[95,96]
		Liposomal verteporfin	Visudyne	Age-related macular degeneration, pathologic myopia, ocular histoplasmosis	i.v.	Approved	[95,96]
		Cationic liposome functionalized anti-transferrin receptor (encapsulated wild type p53 sequence)	SGT-53 SynerGene Therapeutics	Glioblastoma, solid tumour	i.v.	Phase-l/ll	[97]
		Liposomal cytarabine	DepoCyt	Malignant lymphomatous meningitis	i.t[c)]	Approved	[95,96]
		Liposomal daunorubicin	DaunoXome	HIV[d)]-related Kaposi's sarcoma	i.v.	Approved	[95,96]
		Liposomal morphine	DepoDur	Postsurgical analgesia	Epidural	Approved	[95,96]
	PEG[e)]	PEG-camptothecin	Prothecan	Various cancers	i.v.	Phase I/II	[95,96]
		PEG-adenosine deaminase	Adagen	Severe combined immuno-deficiency disease associated with ADA[f)]deficiency	i.m.[g)]	Approved	[95,96]
		PEG-anti-VEGF[h)] aptamer	Macugen	Age-related macular degeneration	i.r.[i)]	Approved	[93,94]
		PEG-granulocyte colony-stimulating factor	Neulasta	Neutropenia associated with cancer chemotherapy	S.C.[j)]	Approved	[93,94]
	Lipid	Perflutren lipid microspheres	Definity	Ultrasound contrast agent (transcranial injuries, stroke)	i.v.	Approved	[97]
		Lipid NPs (RNAi based therapy for knockdown of disease causing TTR protein	Partisiran	Amyloidosis, TTR[k)] knock-down can lead to nerve regeneration	i.v.	Phase I/I/III	[97]
	Dendrimers	Poly L-lysine dendrimers	VivaGel	Antimicrobial protection against genital herpes and HIV infection	Topical	Phase I	[93,94]
	Copolymer	L-Glutamicacid, L-alanine, L-lysine, and L-tyrosine	Copaxone	Multiple sclerosis	s.c.	Approved	[93,94]
Other NP Platforms		Nanocrystalline 2-methoxyestradiol	Panzem NCD	Various cancers	Oral	Phase I	[93,94]
		Silica NPs with NIR fluorophore, PEG Coating, ^{124}I –radiolabelledcRGDY targeting peptide	Cornell Dots	Imaging of melanoma and malignant brain tumour	i.v.	Phase 0	[97]

Nanoparticle-based Platform	Composition	Trade Name	Therapeutic	Administration	Status	Ref.
	Nanocrystalline sirolimus	Rapamune	Immunosuppressant	Oral	Approved	[93,94]
	Nanocrystalline fenofibrate	Tricor	Anti-hype rlipidemic	Oral	Approved	[93,94]

a) intravenous

b) transmembrane carrier systems

c) intrathecal

d) human immunodeficiency virus

e) polyethyleneglycol

f) adenosine deaminase

g) intramuscular

h) vascular endothelial growth factor

i) intravitreous

j) subcutaneous

k) transthyretin.

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Table 4.

Neuroscience offers many challenges to understand the way the brain functions during different action and mental states.

What is the main functional circuitry diagram to perform a particular function?
How do neurons communicate and organize themselves in ordered networks?
How do the paths of information flow?
What are the alternative pathways involved in producing similar outputs and functions?
When are signals transferred from one brain region to another over time?
How are programs organized and reprogramed during the signalling process?
Where is the commanding region, and how does it control the order?
How do memory activity patterns change?
How does the brain respond during exposure of different stimuli, e.g., physical, chemical and biochemical?
What are the penetration behaviors of drugs and chemicals in the BBB?
What is the nature of endothelial cells in the BBB?
What is the nature of interactions between nanomaterials and neuronal membranes?
What are the toxicity profiles of nanomaterials, and how do they need to be resolved for improved neuroscience applications?
How can we effectively deliver treatments for various neurological disorders that affect many people's lives?