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Role of nanotechnology in neurosurgery: A review of recent advances and their applications

Javed Iqbal [a,c], Evan Courville [b,c], Syed Faraz Kazim [b,c], Michael Kogan [c], Meic H. Schmidt [b,c], Christian A. Bowers [b,c,*]

[a] School of Medicine, King Edward Medical University, Lahore, Pakistan
[b] Department of Neurosurgery, University of New Mexico Hospital (UNMH), Albuquerque, NM, USA
[c] Bowers Neurosurgical Frailty and Outcomes Data Science Lab, Albuquerque, NM, USA

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1. Introduction

Nanotechnology, with its focus on developing materials and devices under 100 nm, is revolutionizing various industries, especially in medicine.[1] Its relevance in medicine is underscored by the fact that nanoparticles (NPs) are comparable in size to cellular components. This similarity facilitates a wide range of medical applications, ranging from drug delivery, biomarker discovery, to the modulation of cellular activity.[1] This synergy between nanoscale engineering and biological systems opens up new avenues for medical innovation and therapeutic strategies. Particularly in neurosurgery, the use of nanoparticles is gaining momentum, offering novel tools for both the diagnosis and treatment neurologic conditions.

The intersection of nanotechnology and neurosurgery, while less established than other medical fields, is demonstrating significant potential through recent advancements.[2] These developments, including targeted delivery systems for treatment, improved imaging technologies, strategies for neuroprotection against oxidative stress, nerve repair methodologies, early detection of neurodegenerative diseases, and nerve modulation through the use of nanofibers and nanowires.[3] These advancements not only enhance our understanding of neurological diseases but also pave the way for more precise and effective treatments.

This review article highlights the growing impact of nanomedicine in the field of neurosurgery.[2–4] It delves into the latest research and literature, providing insight into how these advanced technologies are poised to significantly transform neurosurgical practices.

2. Discussion

Nanomedicine, the integration of nanotechnology with medicine, utilizes a range of nanoparticles, and are instrumental in advanced imaging techniques, diagnostic tools, tissue engineering, drug delivery systems, pharmaceutical therapeutics, and implantable devices.[5] Some of the nanoparticles used in research include micelles, liposomes, polymer nanoparticles, dendrimers, carbon nanotubes, metallic nanoparticles, perfluorocarbons, gadolinium complexes, fullerenes, silicon particles, iron oxide, and gold particles.[5,6] (Fig. 1)[7] These NPs exhibit remarkable potential in medical applications, such as imaging techniques, diagnostic tools, tissue-engineered constructs, drug delivery systems, pharmaceutical therapeutics, and implants.[8–11]

3. Role of nanotechnology in neurosurgery

3.1. CNS drug delivery systems

The treatment of brain disorders has historically been challenging, particularly due to the protective mechanisms of the brain, notably the blood–brain barrier (BBB) and the blood-cerebrospinal fluid barrier (B-

* Corresponding author. , Department of Neurosurgery, University of New Mexico, Department of Neurosurgery MSC10 5615, Albuquerque, NM 87131, USA.
E-mail address: christianbowers4@gmail.com (C.A. Bowers).

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CSFB). These barriers, while crucial for protecting the brain from harmful substances, significantly hinder the effective delivery of therapeutic drugs.[2,12] NPs have emerged as a revolutionary tool in this context, serving as efficient nanocarriers that facilitate targeted delivery across these barriers.[7,11] A notable advantage of NPs is their ability to efficiently deliver drugs across the BBB at substantially lower serum concentrations compared to conventional dosages, thus reducing peripheral toxicities while preserving therapeutic efficacy.[11]

The spectrum of nanomaterials being explored is diverse, encompassing liposomes, dendrimers, carbon nanotubes, nano-micelles, polymersomes, gold NPs, nanogels, quantum dots, and magnetic NPs.[2,7,11] A defining characteristic of these nanomaterials is their high surface-to-mass ratio, which is a critical factor in their ability to bind, absorb, or carry other molecules.[7] This property is particularly beneficial in drug delivery, enabling the customization of nanoparticles through the attachment ligands.[13] Such functionalization not only allows for more precise delivery of therapeutic agents to targeted sites but also permits the modification of the pharmacokinetics of the drugs.[11] This is of great interest in the pharmaceutical industry since only a few brain-targeting drugs have achieved market success.[12,14]

NPs can deliver drugs to targeted sites in a controlled manner, making them a promising treatment option for diseases like Alzheimer's, Parkinson's, tumors, and stroke.[5,11,15] Polymeric NPs are typically recommended for most drug delivery systems.[8,16]

Various types of NPs have been utilized for drug delivery systems to treat different neurological diseases. For instance, lipophilic NPs, capable of crossing the BBB, have been effective in delivering levodopa to the CNS in Parkinson's disease[17] Polymorphic micelles, with their distinctive core–shell structure, offer another innovative solution. The outer shell of these micelles prevents drug interactions with serum proteins and non-target cells, while the core is designed to hold water-insoluble drugs.[18] A noteworthy study by Ding et al demonstrated enhanced BBB transport of vinpocetine using oral delivery of mixed micelles.[19]

Additionally, NPs and nanocarriers have demonstrated the ability to effectively deliver chemotherapeutic agents in cases of malignant brain cancer, slowing disease progression.[20]

3.2. Nanoparticles and neuro-regeneration

The nervous system has a limited capacity for self-repair, which poses significant challenges for scientists and physicians. This limited regenerative capacity is one of the main obstacles in treating neurological disorders and injuries. Stem cells possess the ability to self-renew and differentiate into various cell types, making them a promising source for regenerating damaged neurons. Consequently, stem cells are being used in innovative approaches for neural cell replacement and regeneration. However, several other factors, including complex synaptic connections and inhibitory proteins secreted by glial scar cells, also play a role in the regenerative capacity of neurons in the CNS and peripheral nervous system (PNS). Research is ongoing, one major challenge is effectively incorporating neural stem cells at the site of injury, directing their regeneration, and modulating the immune response associated with neuronal injury.[15,21]

The incorporation of NPs and scaffolds can enhance the differentiation of neural stem cells into functional neurons after injury.[22] In a study by Li et al on mouse models, spinal cord injury was induced, and neural stem cells were grafted using a collagen microchannel scaffold enhanced by the use of NPs: drug-loaded encapsulated liposomes. This facilitated the targeted, sustained release of drugs creating a microenvironment for neuronal differentiation of stem cells, motor and sensory neuron regeneration, and axon extension; leading to improved motor-evoked potential and hind-limb locomotion recovery.[22] NPs used in modulating the immune response have proven results so their use in autoimmune and inflammatory conditions is on the rise.[23] A study conducted by Jeong et al studied the effects of intravenous immune modifying NPs as a therapeutic agent for spinal cord injury in mice.[24] In a study on adult beagle dogs with complete spinal cord injury, mesenchymal stem cells with a gelatin scaffold were used. The mesenchymal cells differentiated into neuron-like cells and seemed to contact each other through synapse structures. The study showed that the mesenchymal-derived neural network demonstrated gradual improvement in lower limb motor function. This study highlights the potential of mesenchymal stem cells and scaffolds for neural regeneration in larger animals and provides a promising avenue for future research in human spinal cord injury.[25]

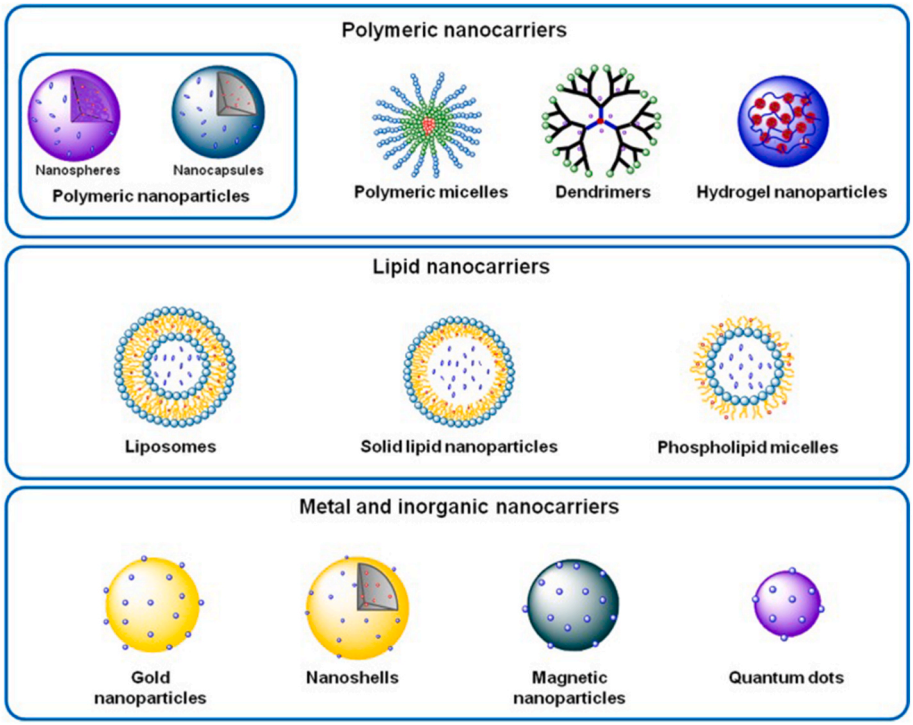

Fig. 1. Examples of Nanoparticles (Conniot J et al.[7] Cancer immunotherapy: nanodelivery approaches for immune cell targeting and tracking. *Front Chem*).

Magnetic NPs, characterized by a magnetic core with an organic or inorganic shell, are currently being studied for their role in central as well as peripheral nerve diseases.[26] They offer several advantages including: the ability to increase the in vivo half-life of neurotrophins and growth factors, facilitate receptor-mediated targeted delivery across the BBB, remotely guided by external magnetic fields, and to manipulate many intracellular signaling pathways.[26]

3.3. Nanoparticles and neuro-oncology

One of the primary obstacles encountered by researchers and neuro-oncologists is devising therapeutic strategies that can effectively permeate the BBB since aggressive tumors such as glioblastoma multiforme (GBM) often exhibit resistance to conventional treatments like chemotherapy and radiation therapy.[27] This resistance arises partly from the BBB's capacity to selectively prevent a majority of chemotherapeutic agents from accessing the tumor site, thereby constraining their efficacy.[27]

Recent advancements in nanotechnology have led to the development of NPs as potential diagnostic and therapeutic tools in the field of neurological cancers. Research has demonstrated that using 186-Rhenium liposomes in brachytherapy for GBM led to a heightened radiation dose targeting the tumor as opposed to radiation therapy alone.[28] This highlights the potential of NPs as a targeted delivery system for cancer therapies, enhancing the therapeutic impact while minimizing adverse effects.[28]

Presently, there are FDA-approved NPs employed in the diagnosis and management of brain tumors (Fig. 2).[56] One example is gold NPs (AuNPs), which can cross the BBB without causing severe damage, due to their small size. Investigations are underway to explore their potential as a therapeutic option. For example Bredlau et al reported the use of AuNPs conjugated with temozolomide as a promising treatment option for malignant glioma.[29] In a study by Salazar-García et al, the impact of AgNPs on rat glioma cells was assessed by combining them with zinc chloride and examining the cytotoxicity of the particles on the glioma cells.[30] (Fig. 3)

3.4. Neuroimaging

Due to the limitations of conventional organic dyes, investigations are now focusing on the unique quantum mechanical properties of NPs for imaging and diagnostic applications.[31] Quantum dots (QDs), a rapidly advancing type of NP, possess unique electrical, thermal, and optical properties, making them ideal for neuroimaging purposes. These particles comprise a metal core, a non-reactive zinc sulfide layer, and an outer coating that can be tailored for specific functional requirements. QDs offer enhanced signal detection compared to traditional fluorescent visualization techniques.[32] A key advantage of QDs in neuroimaging is their broad absorption yet narrow emission spectrum, which results in a higher extinction coefficient for a similar quantum yield, yielding a brighter and more accurate signal.[33] Although no major breakthroughs have been made regarding QDs for tracking neural tissue cells, they have demonstrated in vitro utility for various cell types and tracking within live cells.[34] Additionally, there is a growing understanding of how to utilize QDs by understanding the dynamics of neural receptors. A study by Dahan et al demonstrated the capability of QDs in attaining single-particle tracking within minutes, by facilitating the analysis of the spinal glycine receptor diffusion in real-time.[35] This shows the potential of QDs in studying neural receptors and how they interact with other molecules, which can provide a deeper understanding of how brain tumors and other neural disorders develop and progress. This approach also has the potential to be used in the development of new treatments, as well as in the monitoring of treatment efficacy.

In another experiment, QDs were combined with B-nerve growth factor and this combination was observed to interact with the TrkA receptors in PC-12 cells, which are derived from rat pheochromocytoma. This study suggests that QDs have the potential to be used in the development of new therapies for neurodegenerative disorders and injuries by promoting nerve regeneration and repair. Furthermore, the ability of QDs to target specific cells, such as TrkA receptors, makes them a valuable tool for the diagnosis and management of brain tumors and other neural disorders in the future.[36]

Another category of NPs that are being used in neuroimaging are magnetic NPs, such as Superparamagnetic iron oxide (SPIO) NPs and ultrasmall SPIO (USPIO). These magnetic NPs function as contrast enhancers, augmenting the visualization of brain structures and lesions when integrated with magnetic resonance imaging (MRI) technology.[37] Studies are being conducted to focus on how nanoparticles can contribute to understanding different neuropathologies. Notably, introducing USPIO into human neural precursor cells has demonstrated non-toxic effects on the cells, while also enabling their visualization through MRI. Furthermore, the MRI visualization was dose-dependent, thus supporting the role of USPIO in neuroimaging even more. This means that by adjusting the dose of USPIO NPs, researchers can get a better image of the brain and the specific area of interest. This ability to fine-tune the imaging process allows for more accurate diagnosis and monitoring of brain tumors and other neural disorders.[38] To maximize the potential of NPs, it is crucial to achieve SPIO labeling within a specific time frame. A study by Kim et al presented a rapid labeling method utilizing SPIO NPs conjugated with 2-aminoethyl-ammonium (TMA), yielding SPIO-TMA. This composite product demonstrated accelerated efficacy while circumventing complications associated with vector internalization, thereby eliminating the requirement for a transfection reagent.[39] Even though their unique properties were helpful in

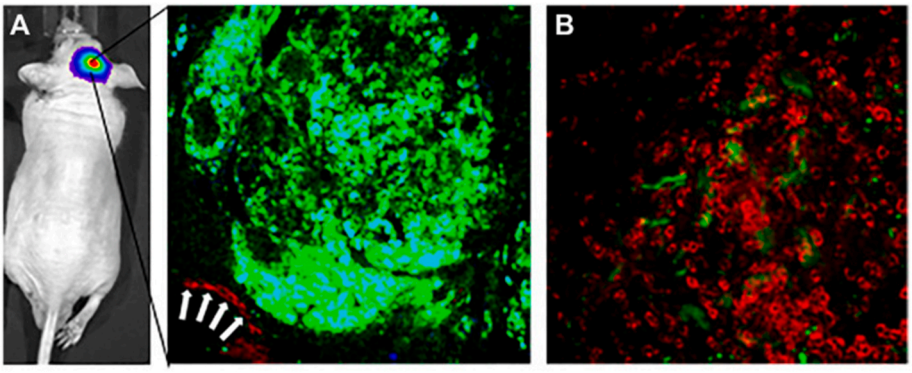

Fig. 2. Intravital multiphoton imaging demonstrates delivery of fluorescent tumor-targeting liposomal nanoparticles across the blood–brain barrier to a glioma brain tumor in an intracranial orthotopic xenograft mouse model of glioma|(Lam FC et al.[56] Integrating Nanotechnology in Neurosurgery, Neuroradiology, and Neuro-Oncology Practice-The Clinicians' Perspective. *Front Bioeng Biotechnol*).

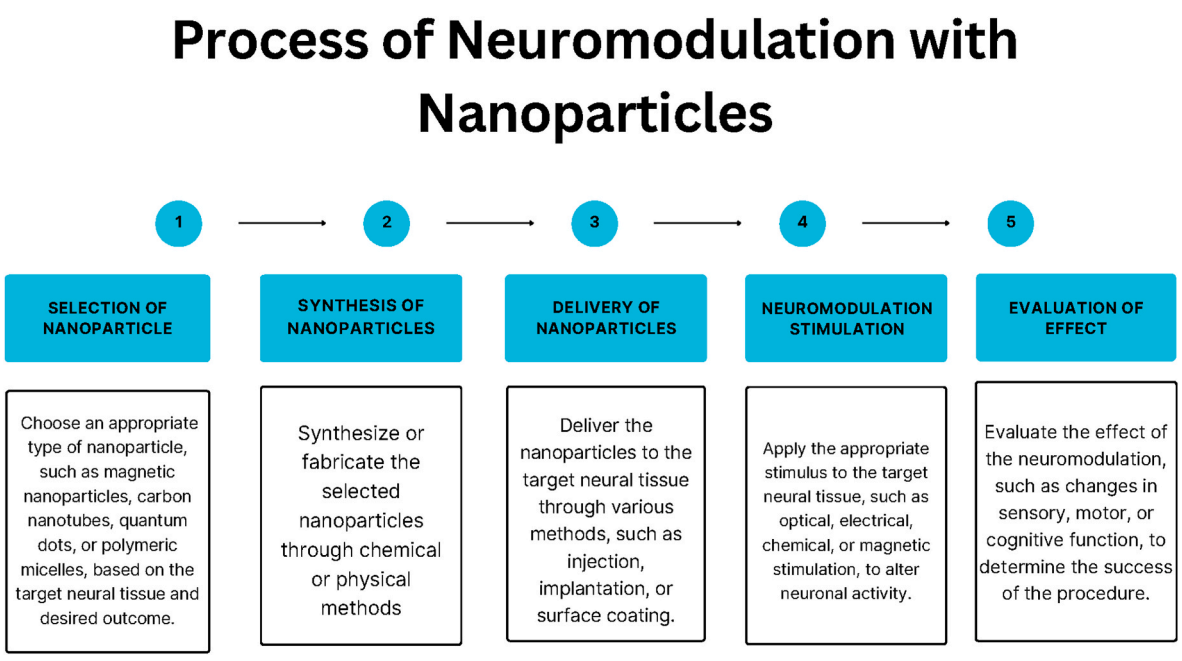

Fig. 3. Process of neuromodulation.

improving cell tracking in vivo, there are still a number of limitations that need to be explored before completely utilizing magnetic NPs for neuroimaging.

3.5. Neuromodulation

Neuromodulation involves altering the activity of neuronal cells by applying an optical, electrical, chemical, or magnetic stimulus to targeted neural tissue. The goal is to achieve highly precise and minimally invasive modulation of different cells and neural circuits with high spatiotemporal resolution. Although this goal has not yet been fully achieved, neuromodulation has been shown to improve and restore sensory, motor, and cognitive functionality. It is considered an effective method for understanding and monitoring brain function as well as for modulating the activity of dysfunctional neural structures to help improve disease progression.[40]

One of the promising nanomaterials that have emerged is carbon nanotubes (CNTs). CNTs can be used to modulate neurite elongation in cell culture and improve regeneration after injuries to the spinal cord in vivo. They can also help modulate the structural and functional characteristics of astrocytes in cell culture. According to a study by Ni et al, CNTs were found to be effective modulators of neuronal growth in cultured neurons. Being water-dispersible, they can be delivered as a diffusive agent in the aqueous medium of the extracellular space of the brain, helping to mediate neurite outgrowth. CNTs can also be modified with polyethylene glycol (PEG) or poly-m-aminobenzene sulphonic acid (PABS) to increase their dispersibility in aqueous media. This research highlights the potential of CNTs and other nanomaterials to improve neuromodulation in neurology and neurosurgery.[41]

According to previous literature and studies, CNTs have been found to be useful for neural cell adhesion and axonal growth.[42,43] A study conducted by Chao et al observed that CNTs were useful in the differentiation of embryonic stem cells into nerve cells.[44] The electrical conductivity of CNTs was also utilized, as electric stimulation has been found to promote neural cell growth.[10]

3.6. Nanoparticles role in aneurysm management

Cerebral aneurysm formation initiates with endothelial injury, leading to pro-inflammatory changes and dysfunctional vascular remodeling.[44] In the context of inflammation, ultrasmall superparamagnetic iron oxide particles (USPIOs) are explored as a noninvasive screening tool for cerebral aneurysms. USPIOs, composed of an iron oxide core with a hydrophilic coating, accumulate in macrophages and can be used as MRI contrast agents for actively inflamed tissues.[45] Ferumoxytol, a USPIO approved for anemia in chronic kidney disease patients, shows promise in neuroimaging for detecting unstable cerebral aneurysms. Studies demonstrate its ability to identify macrophages in aneurysm walls through enhanced MRI, with early uptake associated with aneurysm instability and higher inflammatory molecule levels.[46]

PVA (polyvinyl alcohol) particles are commonly used in middle meningeal artery embolization (MMAE) for chronic subdural hematoma (cSDH). Injected PVA particles adhere to the blood vessel wall, causing thrombus formation and triggering inflammatory processes leading to angionecrosis. As a non-biodegradable agent, PVA is considered a permanent occlusion method; however, recanalization may occur through angiogenesis within the original thrombus weeks to months later. Schwarz et al's study with PVA particles (250–350 μm) for postoperative prophylaxis showed a higher recurrence rate in the subdural evacuating port system group, aligning with previous findings.[47] Ng et al, using smaller PVA particles, demonstrated improved hematoma reduction with adjunctive MMAE to twist-drill craniotomy.[48]

Embosphere (Merit Medical) has been used as a particle embolic agent in recent studies alongside coiling, departing from the more typical use of PVA in prior clinical research.[49] While PVA particle size ranges from 150 to 250 μm, Embosphere sizes typically range from 300 to 500 μm in MMAE for chronic subdural hematoma (cSDH). Tiwari et al were among the first to apply Embosphere in an MMAE-alone approach, reporting no recurrences or complications at a 6-month follow-up.[50] Gomez-Paz et al's study on 23 patients treated with Embosphere and coil embolization revealed a time-to-resolution of midline shift, suggesting a potential relationship with preprocedural baseline.[51] The use of Embosphere in MMAE shows promise as an alternative with positive efficacy and safety outcomes.

3.7. Limitations

Despite encouraging results in tumor-bearing animals, clinical trials comparing liposomal encapsulated cytotoxic treatments to conventional formulations have not consistently demonstrated enhanced

effectiveness in humans. This emphasizes gaps in our understanding of the pharmacokinetics and pharmacodynamics of nanomedicines in humans, underlining the importance of more studies.[52]

The long-term implications of NP deposition in human organs are unknown because most research are based on animal models that show increased cellular oxidative stress in different organs. Toxicity mechanisms may include DNA damage, protein changes, and membrane disruption.[53] Furthermore, preclinical research has linked nanoparticles to neurotoxicity, particularly in interactions with glial cells and neurons. These interactions can result in oxidative bursts, inflammation, DNA damage, and apoptosis. Before contemplating the therapeutic application of nanomedicines, particularly those targeting the central nervous system (CNS), the possible neurotoxic consequences must be extensively explored.[54]

Furthermore, the transition from preclinical investigations to large-scale clinical manufacturing raises difficulties. Most preclinical research produce NPs in non-GLP/non-GMP laboratory conditions, making it impossible to assess the safety and efficacy of nanomedicines in people without understanding the effects of large-scale manufacturing on the final product's quality and consistency.[55]

4. Conclusion

Nanotechnology has the potential to revolutionize current treatment strategies by introducing novel molecular tools that can effectively target pathological tissues while minimizing collateral damage to adjacent structures. Although many nanotechnology-based therapeutic approaches are still in their experimental stages, it is anticipated that breakthroughs in this field will significantly impact various neurosurgical domains for the treatment of CNS neoplasms, neurodegenerative diseases, and vascular and traumatic injuries.

CRediT authorship contribution statement

Javed Iqbal: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft. **Evan Courville:** Formal analysis, Methodology, Writing – original draft. **Syed Faraz Kazim:** Project administration, Supervision, Writing – review & editing. **Michael Kogan:** Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. **Meic H. Schmidt:** Investigation, Project administration, Supervision, Validation. **Christian A. Bowers:** Methodology, Project administration, Supervision, Validation.

Declaration of competing interest

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

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Abbreviations

AgNPs: Silver Nanoparticles
AuNPs: Gold Nanoparticles
BBB: Blood–Brain Barrier
B-CSFB: Blood-Cerebrospinal Fluid Barrier
CNS: Central Nervous System
CNTs: Carbon Nanotubes
GBM: Glioblastoma Multiforme
MRI: Magnetic Resonance Imaging
NPs: Nanoparticles
PABS: Poly-m-aminobenzene Sulphonic Acid
PEG: Polyethylene Glycol
PLGA: PEGylated Poly Lactic-co-glycolic Acid
PNS: Peripheral Nervous System
QDs: Quantum Dots
SPIO: Superparamagnetic Iron Oxide
TBI: Traumatic Brain Injuries
TMA: 2-aminoethyl-ammonium