

Nano-enabled theranostics for brain infections: Exploring the potential of nanoparticles and graphene

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ABSTRACT

Study aiming at formulating viable treatments for neurological disorders is intensifying in the context of their increasing prevalence. Common neurological illnesses that remain difficult to treat include ischemic stroke, glioma, neurodegenerative diseases, and traumatic brain injury. So, the blood-brain barrier (BBB), which is a very selective semipermeable membrane, keeps small molecules, proteins, and oligonucleotides from working as medicine. The blood-brain barrier (BBB), which encases the brain, protects its intricate microenvironments. Due to their ability to selectively transport pharmaceuticals across the blood-brain barrier, multifunctional nanomaterials have emerged as appealing carriers for targeted drug delivery to the brain. Graphene-based nanomaterials exhibit exceptional optical, mechanical, and biological properties. Due to their conductivity, they can serve as a substrate in tissue engineering, facilitate neural connections, and guide the growth and differentiation of neurons. Consequently, graphene-based nanomaterials represent an emerging domain in regenerative medicine. Active targeting utilizes nanostructures with exceptional receptor selectivity and targeting precision, making them ideal payloads for traversing the blood-brain barrier. Microorganisms can efficiently traverse the blood-brain

barrier and assimilate nanoparticles exhibiting biomimetic characteristics. This study focuses on a wide range of traditional diagnostic methods as well as important nanoparticles, including polymers, lipids, gold, and carbon nanotubes, that can cross the blood-brain barrier and help find meningitis and brain infections early. Furthermore, it highlights medication delivery methods utilizing nanotechnology for the study of cerebral infections, including meningitis. The construction and function of the BBB are highlighted in this study, along with the potential of nanotechnology to transcytose into the brain, which may aid in the treatment of neurological disorders.

Keywords: *Nanoparticles, blood-Brain Barrier (BBB), graphene-based nanomaterials, neurodegenerative diseases, drug delivery*

INTRODUCTION

Brain infections can be caused by bacteria, fungus, protozoa, parasites, and prostate viruses. Acute meningitis is frequently caused by bacteria (*Streptococcus pneumoniae*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Haemophilus influenzae*, and *Listeria monocytogenes*) and viruses (mostly Enteroviruses HIV, herpes simplex viruses (HSV), and mumps virus) (Tunkel et al., 1993). Brain infections frequently affect other areas of the central nervous system, such as the spinal cord. Infection can also result from inflammation of the brain and spinal cord's tissue layers (Woehrl et al. 2011). Necrosis, reduced blood and cerebrospinal fluid (CSF) flow, and compromised central nervous system (CNS) functions are all possible outcomes of meningitis. Every age group is susceptible to infectious meningitis, a dangerous central nervous system illness that involves microbial inflammation of the meninges. Bacterial meningitis has an extremely high death and morbidity rate, even following antibiotic and anti-inflammatory treatment. Therefore, bacterial meningitis treatment has been developed in recent decades to both eliminate the invasive germs and break down the resulting inflammatory reaction. The European Federation of Neurological Societies (EFNS) guidelines state that the current therapy of choice

for non-infected adult patients with bacterial meningitis is a combination of corticosteroids and bacteriolytic E-lactam antibiotics (Chaudhuri et al. 2008). Lumbar puncture (LP), also known as spinal tap, is the current diagnostic method for meningitis. During this technique, a tiny volume of CSF is obtained for testing for bacterial and viral infections. Post-LP headache, infection, hemorrhage, cerebral herniation, back discomfort, late-onset epidermoid tumors of the thecal sac, and mild neurologic symptoms including radicular pain are among the possible consequences (Engelborghs et al. 2017). Future individuals with bacterial meningitis contracted in the community may find antibody adjuvant therapy to be a good choice. The development of nanotechnology has demonstrated that the diagnosis of brain infections and meningitis can be effectively treated with nanosensors and nanomaterials (Kischkel et al. 2020). Some characteristics of the nanoparticles include their easy functionalization, simple synthetic method, ability to cross cell membranes, increased drug release at the site of infection due to a higher surface-to-volume ratio, ability to kill the pathogens by inhibiting multiple bacteriological targets, and, most importantly, biological safety (Barani et al. 2021).

It is important to pay particular attention to the blood-brain barrier (BBB). Many therapeutic substances cannot enter the brain from the circulatory system because of the BBB. This is mostly because of ATP-binding cassette proteins called ABC transporters, which make treating brain illnesses difficult (Pereira et al. 2017). There are a number of ways to transport drugs to the brain, but the majority have drawbacks such high risk, high expense, and incompatibility (Ahlawat et al. 2020). In numerous brain-specific treatments, carbon nanotubes (CNTs) have shown great promise as therapeutic agents and nanocarrier systems (Wong et al. 2013; Li et al. 2011). More specifically, CNTs were able to create interfaces with neurons and readily traverse the blood-brain barrier (Ma et al. 2018; Kafa et al. 2015). CNTs do have certain drawbacks, though, such as their toxicity, the inability to manage their length, and their high production costs (Liu et al., 2013; Francis et al. 2018). However, graphene-based materials and carbonaceous zero-dimensional carbon nano-onions have already been

shown to have anti-neurodegenerative properties (John et al. 2015; Mendonca et al. 2015; Pakhira et al. 2016; Plonska-Brzezinska 2019). However, there are several drawbacks to employing those minerals in their pure forms, such as the inability to create well-dispersed aqueous solutions because of their hydrophobic character. For these materials to be used in biomedical applications, additional surface modification is also required (Wu et al. 2019). Here, we describe the application of graphene quantum dots (GQDs) as brain drug nanocarriers that are appropriate for bioimaging because of their capacity to dissolve protein clumps that lead to neurodegenerative disorders and traverse the blood-brain barrier (Gómez et al. 2024).

Nanomaterials and nanoparticles for the treatment of neurological disorders:

Polymeric nanoparticles:

In order to bind, adsorb, dissolve, and encapsulate medications or therapeutic chemicals, polymeric nanoparticles (NPs) are solid colloidal particles that incorporate macromolecular components. Drug delivery methods for treating neurological diseases frequently use degradable polymeric nanoparticles (NPs) with a diameter of 10–100 nm. The two variable units of these particles are nanospheres and nanocapsules (Fornaguera et al. 2016; Das et al. 2016; Soppimath et al. 2001; Pisani et al. 2009; Kreuter 2014). Coreshell NPs make up nanocapsules, while homogeneous matrices are seen in nanospheres. These particle sizes allow for fine-tuning to achieve desired characteristics, such as the preservation of active compounds with simple administration and the penetration of pharmaceuticals into the target cells with increased efficacy and efficiency at cheap production costs (Jain 2012; Neha et al. 2013; Lee et al. 2009). Furthermore, the appropriate rate of disintegration and the particles' ability to penetrate the blood-brain barrier and enter the central nervous system make them effective (Wilson 2009).

Solid Lipid Nanoparticles

For brain targeting, SLNs are seen as an appealing colloidal drug delivery technology. The use of SLNs for targeted

medication delivery in the brain is restricted by their accumulation in the reticuloendothelial system. The lipid matrix has a distinct size, is solid at room temperature, and has the advantage of being a nanocarrier, which improves drug release and stability without having harmful effects on the tissue (Roney et al. 2005). The SLNs have greater advantages in terms of scale-up feasibility and reproducibility through the use of numerous techniques. For other formulations without organic solvents, it is likewise a good choice. Additionally, this lessens the possibility of lingering contamination. These characteristics make SLN one of the most promising drug delivery methods for the treatment of cancer and a variety of neurological diseases (Cacciatore et al. 2016; Sozio et al. 2015; Gastaldi et al. 2014).

Gold Nanoparticles

Better biocompatibility, simple surface functionalization, and facile and efficient transport to target cells and tissues are only a few of their many noteworthy qualities. According to some research, modest microwave field exposure in brain tissue can assist gold nanoparticles (NPs) break down and dissolve A β fibrils and plaques, which can be used to treat AD illness. A β fibrils and plaque buildup in the brain are major symptoms of AD that can be avoided or eliminated (Siddiqi et al. 2017).

Carbon Nanotubes

Iijima made the discovery of the carbon nanotube (CNT) in 1991 (Iijima 1991). Ultra-light weight, high flexibility, low deposition, low cost, high capability, ultra-strong, and inert with electrical and thermal conductivity are only a few of their numerous advantageous qualities. Due to its unique and beneficial qualities for treating neurological conditions, such as AD, PD, and ischemic stroke, it has currently become one of the most promising novel NMs (Komane et al. 2016; Kakkar et al. 2015; Folch et al. 2016). Numerous conditions, including cancer, rheumatoid arthritis, osteoporosis, and bone implants, have been successfully treated with CNTs as drug delivery vehicles in vivo (Kakkar et al. 2015; Malarkey et al. 2007; Siddiqi et al. 2018).

Advantages of metal oxide-based nanoparticles

These NPs, or nanomedicine, can be utilized to diagnose life-threatening illnesses because of their amazing qualities, which include antibacterial action, anti-insecticidal activity, and nontoxicity. Because cerium nanoparticles are unstable in living things, their application is restricted, despite the fact that they can aid in the fight against cancer and AD (Singh et al. 2021). According to Kievit and Zhang (2011) and Tomitaka et al. (2015), iron oxide nanoparticles also demonstrated excellent qualities in the therapy of GBM. However, further research is required to develop metal and metal oxide nanoparticles for effective treatment of central nervous system illnesses (Singh et al. 2021; Annu et al. 2022).

Structure and function of the BBB in healthy and diseased brains

For functional synaptic signaling pathways that govern motor skills, memory, and several other activities, the BBB shields the brain's microenvironment from external effects (Dias et al. 2022). BBB penetration while minimizing off-target effects is necessary for designing the perfect material for brain therapies. Target selection, cell entrance, even distribution within the brain, and exocytosis from cells and the brain following therapeutic activity are other crucial factors. The brain's normal equilibrium depends on the blood-brain barrier. Encircling cerebral capillaries and microvessels, it is made up of endothelial cells that interact closely with astrocytes and pericytes. Tight junctions (TJs) and adherens junctions (AJs), which form the junction of endothelial cells, form a barrier that envelops the brain (Wilhelm et al. 2014). 99 percent of the brain's capillary and neuronal terminals' abluminal surface is encircled by astrocytes (**Fig. 1**) (Pardridge 1999). The BBB is frequently compromised in neurodegenerative illness, stroke, and traumatic brain injury (TBI). This allows harmful substances to enter the body and alters regular metabolic processes, which results in several defects in the function of astrocytes, neuron cells, and microglia cells (DiPardo et al. 2017). Designing NP-based disease treatment systems requires an understanding of the structure of the blood-brain barrier (McLoughlin et al. 2024).

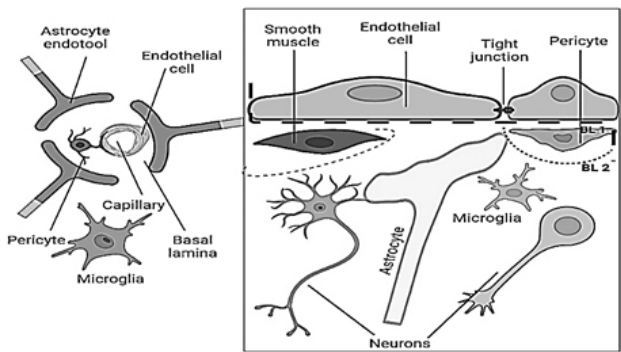


Fig 1. Blood-brain barrier’s structure and composition.

Neurodegenerative diseases and blood-brain barrier

Transcellular-lipophilic diffusive routes, paracellular-tight junctions, transport proteins, receptor-mediated endocytosis, and adsorptive transcytosis are some of the physiological pathways by which substances can pass through the blood-brain barrier (Gonzalez-Carter et al. 2020).

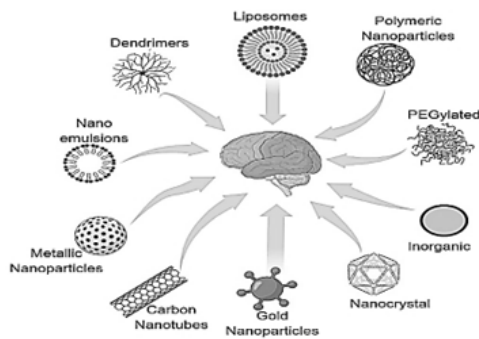


Fig 2. Nanotechnology-based drug delivery systems approach on treatment of CNS disorders.

To improve CNS medication delivery, several transport pathways have been investigated. Transient BBB disruption is one of the more specialized neurosurgical drug delivery techniques that may be useful in treating CNS disorders. Among the different therapeutic approaches, therapeutic systems based on nanomedicine offer a fresh approach to delivering beneficial substances with encouraging pharmacokinetics to boost the effectiveness of the medications now on the market to treat CNS diseases (Pardridge 1998; Nguyen et al. 2021).

Antimicrobial activity of graphene materials

Role of material physicochemistry-

Nanotoxicological effects on microbial cells are referred to as the antibacterial activity of nanomaterial systems. The antimicrobial activity of GMs is therefore dependent on their nanoscale structures and physicochemical properties, including dimensions, solubility, dispersability in solutions (in relation to surface charges and aggregation behaviors), capability in producing oxidative species, and existence of capping agents in solutions, as has been noted for the nanotoxicity of almost all nanoparticles (Buzea et al. 2007; Ripp et al. 2011). A wide range of structurally and physicochemically diverse materials are referred to be GMs. These materials include pristine graphene (PG), few-layer graphite platelets (GPs), oxidized and reduced variants of PGs and GPs (e.g., GO and rGO), and other compounds linked to graphene, such as GQDs. (Bianco et al. 2013; Wick et al. 2014; Zhen et al. 2018).

Utilization modes of graphene materials

Since antimicrobial GMs are a relatively new field, most of the research that has been published so far is proof-of-concept research categorized into four main themes based on the intended use areas: (i) antimicrobial colloids; (ii) contact-killing surfaces; (iii) release-killing surfaces; and (iv) light-activated disinfectants (also known as photothermal/photodynamic inactivation) (Karahan et al. 2018).

Pathophysiology of meningitis:-

The CNS is protected from blood-borne pathogen invasion by the effective BBB and CSF barrier, as well as an outer layer of leptomeninges and the skull. Therefore, for the CNS infections to enter the brain, they need either a biological host defense gauntlet or an outer membrane defect (such as purulent mastoiditis, post-traumatic or post-neurosurgical dura leak). Multiple pathogen-host interactions that concurrently result in mucosal colonization, invasion, and survival within the intravascular space, as well as blood-brain/CSF barrier crossing, are necessary for effective CNS invasion (Herold et al. 2019).

Application of nanoparticles for improved therapeutics of meningitis

The best chance of obtaining superior meningitis therapy is through distribution approaches based on nanotechnology (Barani et al. 2021). How easily nanoparticles penetrate the skin or barrier depends on their size, charge, and general structure (Sun et al. 2020). The BBB's tightness is mostly caused by the vascular layers of brain capillary endothelial cells, which are connected side by side by adherens and tight junctions. Transcytosis via receptors is the most common way that NPs enter the brain. Using ligands such as transferrin, lactoferrin, antibodies, or surfactants like tween 80, the functionalized NPs can be created. NPs can be released at the opposite region of the membrane when ligands for NPs connect with their receptors on the luminal side of endothelial cells, causing plasma membrane invasions and pinch-free vesicle formation. Efflux pumps may decrease the quantity of NPs that are maintained in the brain parenchyma (Sharma et al. 2021).

Drug delivery methods for the brain

Invasive approach

By breaching the blood-brain barrier, this mechanical method delivers the medication directly into the brains. For the administration of intracranial hemorrhage medicines and intracerebroventricular (ICV) injection, brain surgery is

required (Stenehjem et al. 2009; Gabathuler 2010). The BBB is disrupted for drug diffusion when the endothelial tight junction collapses (Inamura and Black 1994; Stenehjem et al. 2009).

Pharmacological approach

This empirical methodology is based on the spontaneous inactive passage of medications over the blood–brain barrier (Stenehjem et al. 2009; Gabathuler 2010). These substances can pass through the blood–brain barrier on their own because of their small molecular size, low hydrophobic interaction ability, and water solubility (Hsiung et al. 2003). This approach, which enhances drug transport across the blood–brain barrier, also includes physiological modifications, such as a reduction in the quantity of polar functional groups (Pardridge 1998; Rhaman et al. 2022).

Advantages of NP's for brain therapy:-

NPs Have Small Particle Size That Facilitates Their Penetration Across the BBB:

The primary obstacles to treating brain diseases and disorders have been overcoming the blood–cerebrospinal fluid (CSF) and blood–brain barrier (BBB). P-gp carefully mediates the efflux of materials across the blood–brain barrier; therefore, its downregulation is linked to the development of tumors and neurological diseases (Henson et al. 1992; van Assema et al. 2012; Jeynes and Provias 2013). P-gp inhibition enhances a drug's ability to pass the blood–brain barrier and produce its intended effect (Jablonski et al. 2014).

NPs Have Low Toxicity and Can Be Used To Improve the Toxicity of Conventional Drugs in Their Targeted Cells:

The cytotoxicity of the majority of medications affects their therapeutic efficacy. When compared to traditional therapy, NPs cause significantly less brain toxicity. For instance, intranasal delivery of PLGA NPs has been shown to be extremely successful in transporting the mitoNEET ligand inhibitor NL-1 in a brain ischemia/reperfusion paradigm without causing any harm (Saralkar et al. 2020). Additional research has also demonstrated that encapsulating cytotoxic

drugs like sorafenib (an anticancer medication), amphotericin B (an antifungal medication), and Thioridazine (an antipsychotic medication) into NPs significantly raises their toxicity index by improving drug solubility, bioavailability, and sustained release (Tang et al. 2015; Vibe et al. 2016; Li et al. 2020).

Application of NPs in the Treatment Of Brain Diseases and Disorders:-

Huntington's disease (HD), epilepsy, amnesia, ischemic stroke (IS), brain tumor, and amyotrophic lateral sclerosis (ALS) (Ngowi et al. 2021).

Challenges in Brain Immunotherapy Based on Nanomedicine:-

Only a small number of medications, including rivastigmine, memantine, galantamine, tacrine, and donepezil (Birks et al. 2015), are currently used to support the clinical treatment of neurodegenerative disorders (Lammers et al. 2011). The central nervous system (CNS) is the most complex and sensitive structure in the human body, and it is securely packed and sealed by the blood-brain barrier (BBB) and brain cell membrane (BCFB) (Furtado et al. 2018) (Erickson et al. 2013). Because of its complexity, there are many limitations in delivering targeted medications from the blood to the central nervous system (CNS). This includes a lack of information regarding the role of medications, their half-lives, or bio-presences for brain cells, their effects on the CNS, or the irregular and uncertain relationships between off-target medications and receptors and proteins. The unstable index of evaluated medications is made up of the patient's genotype, the complex pharmacology of certain medications, neurodegenerative symptoms, the long latency period and incompetence of medications, the subsequent development of infections, an incorrect number of medications, and a variety of medication reactions. Furthermore, the challenges are made considerably more challenging by issues pertaining to the brain (Fernández et al. 2018; Sharma et al. 2015; Guo et al. 2023).

Graphene-based Nanomaterials (GBNS) as multifunctional drug-delivery system for the nervous system

Chemical modification through the addition of hydroxyl, carboxyl, amino, or other functional groups is made possible by the vast surface area of GBNs (John et al. 2015). As an alternative, noncovalent functionalization (hydrophobic or π - π stacking interactions and hydrogen bonding) can be used to load medicinal compounds into GBNs (Georgakilas et al. 2016). Due to shortcomings in existing therapeutic techniques, such as the poor hydrophilicity of many anticancer drugs, the decreased accessibility of the central nervous system, and the unspecific toxicity of chemotherapy on healthy tissue, research efforts were mostly focused on developing new therapeutics for brain tumors (Arvanitis et al. 2020). In order to treat CNS malignancies with a high mortality rate in children, GBNs were used as nanocarriers (Kaatsch 2010). While the use of harsh treatments already in use can boost survival rates in certain situations (Weil et al. 2017), the long-term and late effects of treating children cancer can be severe and irreversible, resulting in cognitive dysfunctions, emotional disorders, and subsequent neoplasms (Castellino et al. 2014; Marusak et al. 2018; Izycka-Swieszewska et al. 2018). Neuro-oncology in children and adults may benefit from the use of graphene as a drug-delivery nanocarrier (Cellot et al. 2022).

Table 1. Most promising graphene-based nanomaterial applications for neural growth and central nervous system regeneration (Wang et al. 2020)

Graphene-Based Scaffold	Biomedical Applications	Main Results	References
rGO encapsulated on poly (l-lactic acid-co-caprolactone) microfibers (PLCL)	Development of 3D neural networks	Outgrowth of neurite and formation of oriented neuronal-like networks	(Wang et al. 2020)

Laser-Scribed rGO	Generation of micropatterned in vitro neuronal networks	Adhesion and survival of rat primary neurons and guide the subsequent elongation of neurites	(Lee et al. 2018)
Ginseng-rGO sheets	Neural stem cell (NSC) differentiation	Accelerated differentiation of neural stem cells into neurons	(Akhavan et al. 2014)
3D-graphene foam	NSC proliferation and cell fate decision	Enhancement of NSC proliferation through metabolic regulation	(Fang et al. 2020)
Silk/ GO micro/ nano-fibrous scaffold	Nerve regeneration	Enhancement of metabolic activity, Neuronoma NG108-15 cells proliferation and neurite outgrowth	(Magaz et al. 2021)

Clinical advancements in nanomaterials for neurological diseases

APOLLO: Transthyretin-mediated amyloidosis, a rare neurological illness caused by transthyretin misfolding, is presently being treated in phase three clinical trials using Patisiran ALN-TR02, an NP assembly made up of siRNA-loaded lipid NPs (Zhang et al. 2020). The results of the phase three trial were recently published (Quan et al. 2023). Another IONP, the Pulse NanoMed System, is scheduled to undergo a clinical trial (Chung 2023). A Phase 2 clinical trial for guided brain-directed stereotactic radiation therapy is presently underway using gadolinium-based NPs, with completion anticipated in 2026 (MD 2022). They can ascertain whether the NP improves the precision and efficacy of radiation therapy by contrasting stereotactic radiation with regular stereotactic radiation for brain cancers and brain metastases. In 2021, one study investigated enhancing the BBB transport of siRNA-conjugated gold nanoparticles for Bcl2L12 downregulation. Brain metastases from breast cancer and other cancer types

were treated with this medication in a phase 1/2a clinical trial (2B3-101) (Kumthekar et al. 2021; Aftimos et al. 2014; Brandsma et al. 2014; McLoughin et al. 2024).

Table 2. Treatment trials using Nanoparticles for brain diseases and disorders (Lackner et al. 2008)

Nanoparticles	Disease	Mechanisms	Effects	References
Silver Nanoparticles	Acute occlusive hydrocephalus	Ventriculitis caused by catheters is prevented	Enhanced the health of patients	(Lackner et al. 2008)
Magnetic iron oxide nanoparticles + reduced radiotherapy	Glioblastoma multiforme	Increased Caspase-3, heat shock protein, and programmed death ligand 1 levels suppress tumor growth	Enhanced the overall survival rate of patients	(Maier-Hauff et al. 2011; Grauer et al. 2019)
Ultrasmall magnetic iron oxide	Ischemic stroke	Activated macrophages	Targeted inflammatory cytokines more effectively	(Saleh et al. 2007)
Nano-curcumin + omega-3 fatty acid	Migraine	Intercellular adhesion molecule 1, TNF-a, and cyclooxygenase-2/ inducible nitric acid gene expression is suppressed	Relieved headaches	(Abdolahi et al. 2019; Abdolahi et al. 2017; Soveyd et al. 2017)

CONCLUSION AND FUTURE PERSPECTIVES

Conventional medication delivery techniques are unable to penetrate the brain’s complex physiology. Thanks to the advancement of nanotechnology, medications for infections can now be administered by piercing the blood-brain barrier. Nanomaterials have showed a lot of promise due to their flexibility, safety, biodegradation, and biocompatibility. In the modern day, the use of nanoparticles to treat infectious brain diseases is a potential prospect due to recent advancements. By incorporating them into suitable nanostructures,

the molecules with decreased hydrophobicity can also be dispersed. Additionally, the anti-infectious substance can be directly administered through the bacterial surface receptors without posing a threat to the surrounding tissues. But before thinking about therapeutic applications, safety concerns must be addressed in light of the latest developments. In order to treat brain infections and nervous system failure, nanotechnology presents exciting answers to the primary diagnostic problems. The safe, efficient, and targeted delivery of biological substances, such as anti-inflammatory medications, for the diagnosis of infectious diseases, such as meningitis, is a promising use for nanoscale devices. Naturally, diagnostic tools are required to address certain issues, such as the ability to cross the blood-brain barrier, and developments in nanotechnology will improve the capacity to identify brain infections. Working successfully in clinical trials, which will address any potential nanotoxicological difficulties, is the next essential step in developing this subject. Until recently, a significant amount of research in this field has been carried out using different animal models.

Conflict of Interest

There is no conflict of interest related to the study.

Author contributions

Acquisition and interpretation of data is done by Tanisha Bhowmick, Dipti Das, Tiyasha Saha. Conception, design and revising of the article are done by Rupesh Dutta Banik.

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REFERENCES

Abdolahi, M., Jafarieh, A., Sarraf, P., Sedighiyan, M., Yousefi, A., Tafakhori, A., ... & Djalali, M. (2019). The neuromodulatory effects of ω -3 fatty acids and nano-curcumin on the COX-2/iNOS network in migraines: A clinical trial study from gene expression to clinical symptoms. *Endocrine*,

Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders), 19(6), 874-884.

Abdolahi, M., Tafakhori, A., Togha, M., Okhovat, A. A., Siassi, F., Eshraghian, M. R., ... & Djalali, M. (2017). The synergistic effects of ω -3 fatty acids and nano-curcumin supplementation on tumor necrosis factor (TNF)- α gene expression and serum level in migraine patients. *Immunogenetics*, 69, 371-378.

Aftimos, P. G., Diéras, V., Altintas, S., Anders, C., Arnedos, M., Gelderblom, A., ... & Brandsma, D. (2014). Phase I/IIA study with CNS-targeted liposomal doxorubicin (2B3-101) in patients with brain metastases (BM) from breast cancer (BC) and other brain tumors. *Annals of Oncology*, 25, i25.

Ahlawat, J., Guillama Barroso, G., Masoudi Asil, S., Alvarado, M., Armendariz, I., Bernal, J., ... & Narayan, M. (2020). Nanocarriers as potential drug delivery candidates for overcoming the blood-brain barrier: challenges and possibilities. *Acs Omega*, 5(22), 12583-12595.

Akhavan, O., Ghaderi, E., Abouei, E., Hatamie, S., & Ghasemi, E. (2014). Accelerated differentiation of neural stem cells into neurons on ginseng-reduced graphene oxide sheets. *Carbon*, 66, 395-406.

Annu, Sartaj, A., Qamar, Z., Md, S., Alhakamy, N. A., Baboota, S., & Ali, J. (2022). An insight to brain targeting utilizing polymeric nanoparticles: effective treatment modalities for neurological disorders and brain tumor. *Frontiers in Bioengineering and Biotechnology*, 10, 788128.

Arvanitis, C. D., Ferraro, G. B., & Jain, R. K. (2020). The blood-brain barrier and blood-tumour barrier in brain tumours and metastases. *Nature Reviews Cancer*, 20(1), 26-41.

Barani, M., Mukhtar, M., Rahdar, A., Sargazi, G., Thytiadou, A., & Kyzas, G. Z. (2021). Progress in the Application of Nanoparticles and Graphene as Drug Carriers and on the Diagnosis of Brain Infections. *Molecules*, 26(1), 186.

Barani, M., Mukhtar, M., Rahdar, A., Sargazi, G., Thytiadou, A., & Kyzas, G. Z. (2021). Progress in the Application of Nanoparticles and Graphene as Drug Carriers and on the Diagnosis of Brain Infections. *Molecules*, 26(1), 186.

Bianco, A., Cheng, H. M., Enoki, T., Gogotsi, Y., Hurt, R. H., Koratkar, N., ... & Zhang, J. (2013). All in the graphene

family—A recommended nomenclature for two-dimensional carbon materials. *Carbon*, 65, 1-6.

Birks, J. S., & Evans, J. G. (2015). Rivastigmine for Alzheimer's disease. *Cochrane Database of systematic reviews*, (4).

Brandsma, D., Dieras, V., Altintas, S., Anders, C., Arnedos, M., Gelderblom, H., ... & Aftimos, P. (2014). P08. 03 2B3-101, GLUTATHIONE PEGYLATED LIPOSOMAL DOXORUBICIN, IN PATIENTS WITH RECURRENT HIGH GRADE GLIOMAS AND BREAST CANCER BRAIN METASTASES. *Neuro-oncology*, 16(suppl_2), ii50-ii51.

Buzea, C., Pacheco, I. I., & Robbie, K. (2007). Nanomaterials and nanoparticles: sources and toxicity. *Biointerphases*, 2(4), MR17-MR71.

Cacciatore, I., Ciulla, M., Fornasari, E., Marinelli, L., & Di Stefano, A. (2016). Solid lipid nanoparticles as a drug delivery system for the treatment of neurodegenerative diseases. *Expert opinion on drug delivery*, 13(8), 1121-1131.

Castellino, S. M., Ullrich, N. J., Whelen, M. J., & Lange, B. J. (2014). Developing interventions for cancer-related cognitive dysfunction in childhood cancer survivors. *Journal of the National Cancer Institute*, 106(8), dju186.

Cellot, G., Franceschi Biagioni, A., & Ballerini, L. (2022). Nanomedicine and graphene-based materials: advanced technologies for potential treatments of diseases in the developing nervous system. *Pediatric Research*, 92(1), 71-79.

Chaudhuri, A., Martin, P. M., Kennedy, P. G. E., Andrew Seaton, R., Portegies, P., Bojar, M., ... & EFNS Task Force. (2008). EFNS guideline on the management of community-acquired bacterial meningitis: report of an EFNS Task Force on acute bacterial meningitis in older children and adults. *European journal of neurology*, 15(7), 649-659.

Chung, K. J. (2023). Improving the Reliability and Accessibility of CT Perfusion Imaging in Acute Ischemic Stroke.

Das, S., Carnicer-Lombarte, A., Fawcett, J. W., & Bora, U. (2016). Bio-inspired nano tools for neuroscience. *Progress in Neurobiology*, 142, 1-22.

Di Pardo, A., Amico, E., Scalabrì, F., Pepe, G., Castaldo, S., Elifani, F., ... & Maglione, V. (2017). Impairment of blood-brain barrier is an early event in R6/2 mouse model of Huntington Disease. *Scientific reports*, 7(1), 41316.

Dias, I. H., Taiwo, R., & Ma, D. (2022). The blood-brain barrier models to study apolipoprotein E genotypes in Alzheimer's disease. *Neural Regeneration Research*, 17(9), 1973-1974 DOI: 10.4103/1673-5374.331538.

Engelborghs, S., Niemantsverdriet, E., Struyfs, H., Blennow, K., Brouns, R., Comabella, M., ... & Teunissen, C. E. (2017). Consensus guidelines for lumbar puncture in patients with neurological diseases. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, 8, 111-126.

Erickson, M. A., & Banks, W. A. (2013). Blood-brain barrier dysfunction as a cause and consequence of Alzheimer's disease. *Journal of Cerebral Blood Flow & Metabolism*, 33(10), 1500-1513.

Fang, Q., Zhang, Y., Chen, X., Li, H., Cheng, L., Zhu, W., ... & Chai, R. (2020). Three-dimensional graphene enhances neural stem cell proliferation through metabolic regulation. *Frontiers in Bioengineering and Biotechnology*, 7, 436.

Fernández, T., Martínez-Serrano, A., Cussó, L., Desco, M., & Ramos-Gómez, M. (2018). Functionalization and characterization of magnetic nanoparticles for the detection of ferritin accumulation in Alzheimer's disease. *ACS chemical neuroscience*, 9(5), 912-924.

Folch, J., Petrov, D., Ettcheto, M., Abad, S., Sánchez-López, E., García, M. L., ... & Camins, A. (2016). Current research therapeutic strategies for Alzheimer's disease treatment. *Neural plasticity*, 2016(1), 8501693.

Fornaguera, C., & Solans, C. (2016). Polymeric nanoparticles for drug delivery in neurological diseases. *Current pathobiology reports*, 4, 189-197.

Francis, A. P., & Devasena, T. (2018). Toxicity of carbon nanotubes: A review. *Toxicology and industrial health*, 34(3), 200-210.

Furtado, D., Björnmalm, M., Ayton, S., Bush, A. I., Kempe, K., & Caruso, F. (2018). Overcoming the blood-brain barrier: the role of nanomaterials in treating neurological diseases. *Advanced materials*, 30(46), 1801362.

Gabathuler, R. (2010). Approaches to transport therapeutic drugs across the blood-brain barrier to treat brain diseases. *Neurobiology of disease*, 37(1), 48-57.

Gastaldi, L., Battaglia, L., Peira, E., Chirio, D., Muntoni, E., Solazzi, I., ... & Dosio, F. (2014). Solid lipid nanoparticles as vehicles of drugs to the brain: current state of the art. *European Journal of Pharmaceutics and Biopharmaceutics*, 87(3), 433-444.

Georgakilas, V., Tiwari, J. N., Kemp, K. C., Perman, J. A., Bourlinos, A. B., Kim, K. S., & Zboril, R. (2016). Noncovalent functionalization of graphene and graphene oxide for energy materials, biosensing, catalytic, and biomedical applications. *Chemical reviews*, 116(9), 5464-5519.

Gómez, I. J., Křížková, P., Dolečková, A., Cardo, L., Wetzl, C., Pizúrová, N., ... & Zajíčková, L. (2024). Multifunctional graphene quantum dots: A therapeutic strategy for neurodegenerative diseases by regulating calcium influx, crossing the blood-brain barrier and inhibiting A β -protein aggregation. *Applied Materials Today*, 36, 102072.

Gonzalez-Carter, D., Liu, X., Tockary, T. A., Dirisala, A., Toh, K., Anraku, Y., & Kataoka, K. (2020). Targeting nanoparticles to the brain by exploiting the blood-brain barrier impermeability to selectively label the brain endothelium. *Proceedings of the National Academy of Sciences*, 117(32), 19141-19150.

Grauer, O., Jaber, M., Hess, K., Weckesser, M., Schwindt, W., Maring, S., ... & Stummer, W. (2019). Combined intracavitary thermotherapy with iron oxide nanoparticles and radiotherapy as local treatment modality in recurrent glioblastoma patients. *Journal of neuro-oncology*, 141, 83-94.

Guo, Z. H., Khatkhat, S., Rauf, M. A., Ansari, M. A., Alomary, M. N., Razak, S., ... & Ji, X. Y. (2023). Role of nanomedicine-based therapeutics in the treatment of CNS disorders. *Molecules*, 28(3), 1283.

Henson, J. W., Cordon-Cardo, C., & Posner, J. B. (1992). P-glycoprotein expression in brain tumors. *Journal of neuro-oncology*, 14, 37-43.

Herold, R., Schrotten, H., & Schwerk, C. (2019). Virulence factors of meningitis-causing bacteria: enabling brain entry across the blood-brain barrier. *International journal of molecular sciences*, 20(21), 5393.

Hsiung, S. C., Adlersberg, M., Arango, V., Mann, J. J., Tamir, H., & Liu, K. P. (2003). Attenuated 5-HT_{1A} receptor signaling in brains of suicide victims: involvement of adenylyl cyclase, phosphatidylinositol 3-kinase, Akt and mitogen-

activated protein kinase. *Journal of neurochemistry*, 87(1), 182-194.

Iijima, S. (1991). Helical microtubules of graphitic carbon. *nature*, 354(6348), 56-58.

Inamura, T., & Black, K. L. (1994). Bradykinin selectively opens blood-tumor barrier in experimental brain tumors. *Journal of Cerebral Blood Flow & Metabolism*, 14(5), 862-870.

Izycka-Swieszewska, E. et al. Malignant gliomas as second neoplasms in pediatric cancer survivors: neuropathological study. *Biomed. Res. Int.* **2018**, 4596812 (2018).

Jablonski, M. R., Markandaiah, S. S., Jacob, D., Meng, N. J., Li, K., Gennaro, V., ... & Pasinelli, P. (2014). Inhibiting drug efflux transporters improves efficacy of ALS therapeutics. *Annals of clinical and translational neurology*, 1(12), 996-1005.

Jain, K. K. (2012). Nanobiotechnology-based strategies for crossing the blood-brain barrier. *Nanomedicine*, 7(8), 1225-1233.

Jeynes, B., & Provias, J. (2013). P-Glycoprotein Altered Expression in Alzheimer's Disease: Regional Anatomic Variability. *Journal of Neurodegenerative Diseases*, 2013(1), 257953.

John, A. A., Subramanian, A. P., Vellayappan, M. V., Balaji, A., Mohandas, H., & Jaganathan, S. K. (2015). Carbon nanotubes and graphene as emerging candidates in neuroregeneration and neurodrug delivery. *International journal of nanomedicine*, 4267-4277.

John, A. A., Subramanian, A. P., Vellayappan, M. V., Balaji, A., Mohandas, H., & Jaganathan, S. K. (2015). Carbon nanotubes and graphene as emerging candidates in neuroregeneration and neurodrug delivery. *International journal of nanomedicine*, 4267-4277.

Kaatsch, P. (2010). Epidemiology of childhood cancer. *Cancer treatment reviews*, 36(4), 277-285.

Kafa, H., Wang, J. T. W., Rubio, N., Venner, K., Anderson, G., Pach, E., ... & Al-Jamal, K. T. (2015). The interaction of carbon nanotubes with an in vitro blood-brain barrier model and mouse brain in vivo. *Biomaterials*, 53, 437-452.

Kakkar, A. K., & Dahiya, N. (2015). Management of Parkinson's disease: Current and future pharmacotherapy. *European journal of pharmacology*, 750, 74-81.

Karahan, H. E., Wiraja, C., Xu, C., Wei, J., Wang, Y., Wang, L., ... & Chen, Y. (2018). Graphene materials in antimicrobial nanomedicine: current status and future perspectives. *Advanced healthcare materials*, 7(13), 1701406.

Kischkel, B., Rossi, S. A., Santos, S. R., Nosanchuk, J. D., Travassos, L. R., & Taborda, C. P. (2020). Therapies and vaccines based on nanoparticles for the treatment of systemic fungal infections. *Frontiers in cellular and infection microbiology*, 10, 463.

Komane, P. P., Choonara, Y. E., du Toit, L. C., Kumar, P., Kondiah, P. P., Modi, G., & Pillay, V. (2016). Diagnosis and treatment of neurological and ischemic disorders employing carbon nanotube technology. *Journal of Nanomaterials*, 2016(1), 9417874.

Kreuter, J. (2014). Drug delivery to the central nervous system by polymeric nanoparticles: what do we know?. *Advanced drug delivery reviews*, 71, 2-14.

Kumthekar, P., Ko, C. H., Paunesku, T., Dixit, K., Sonabend, A. M., Bloch, O., ... & Stegh, A. H. (2021). A first-in-human phase 0 clinical study of RNA interference-based spherical nucleic acids in patients with recurrent glioblastoma. *Science translational medicine*, 13(584), eabb3945.

Lackner, P., Beer, R., Broessner, G., Helbok, R., Galiano, K., Pleifer, C., ... & Schmutzhard, E. (2008). Efficacy of silver nanoparticles-impregnated external ventricular drain catheters in patients with acute occlusive hydrocephalus. *Neurocritical care*, 8, 360-365.

Lammers, T., Aime, S., Hennink, W. E., Storm, G., & Kiessling, F. (2011). Theranostic nanomedicine. *Accounts of chemical research*, 44(10), 1029-1038.

Lee, K. B., Solanki, A., Kim, J. D., & Jung, J. (2009). *Nanomedicine: dynamic integration of nanotechnology with biomedical science* (pp. 2-39). Pan Stanford Publishing Pte. Ltd..

Lee, S. H., Lee, H. B., Kim, Y., Jeong, J. R., Lee, M. H., & Kang, K. (2018). Neurite guidance on laser-scribed reduced graphene oxide. *Nano letters*, 18(12), 7421-7427.

Li, H., Luo, Y., Derreumaux, P., & Wei, G. (2011). Carbon nanotube inhibits the formation of β -sheet-rich oligomers of the Alzheimer's amyloid- β (16-22) peptide. *Biophysical journal*, 101(9), 2267-2276.

Li, N., Chen, Y., Sun, H., Huang, T., Chen, T., Jiang, Y., ... & Wu, M. (2020). Decreasing acute toxicity and suppressing colorectal carcinoma using Sorafenib-loaded nanoparticles. *Pharmaceutical Development and Technology*, 25(5), 556-565.

Liu, Y., Zhao, Y., Sun, B., & Chen, C. (2013). Understanding the toxicity of carbon nanotubes. *Accounts of chemical research*, 46(3), 702-713.

Ma, X., Zhong, L., Guo, H., Wang, Y., Gong, N., Wang, Y., ... & Liang, X. J. (2018). Multiwalled carbon nanotubes induced hypotension by regulating the central nervous system. *Advanced Functional Materials*, 28(11), 1705479.

Magaz, A., Li, X., Gough, J. E., & Blaker, J. J. (2021). Graphene oxide and electroactive reduced graphene oxide-based composite fibrous scaffolds for engineering excitable nerve tissue. *Materials Science and Engineering: C*, 119, 111632.

Maier-Hauff, K., Ulrich, F., Nestler, D., Niehoff, H., Wust, P., Thiesen, B., ... & Jordan, A. (2011). Efficacy and safety of intratumoral thermotherapy using magnetic iron-oxide nanoparticles combined with external beam radiotherapy on patients with recurrent glioblastoma multiforme. *Journal of neuro-oncology*, 103, 317-324.

Malarkey, E. B., & Parpura, V. (2007). Applications of carbon nanotubes in neurobiology. *Neurodegenerative Diseases*, 4(4), 292-299.

Marusak, H. A., Iadipaolo, A. S., Harper, F. W., Elrahal, F., Taub, J. W., Goldberg, E., & Rabinak, C. A. (2018). Neurodevelopmental consequences of pediatric cancer and its treatment: applying an early adversity framework to understanding cognitive, behavioral, and emotional outcomes. *Neuropsychology review*, 28, 123-175.

McLoughlin, C. D., Nevins, S., Stein, J. B., Khakbiz, M., & Lee, K. B. (2024). Overcoming the Blood-Brain Barrier: Multifunctional Nanomaterial-Based Strategies for Targeted Drug Delivery in Neurological Disorders. *Small Science*, 4(12), 2400232.

MD, A. (2022). *A Double-Blind, Phase II Randomized Study of Brain-Directed Stereotactic Radiation With or Without AGuIX Gadolinium-Based Nanoparticles in the Management of Brain Metastases at Higher Risk of Local Recurrence With Radiation Alone.*

Mendonça, M. C. P., Soares, E. S., de Jesus, M. B., Ceragioli, H. J., Ferreira, M. S., Catharino, R. R., & da Cruz-Höfling, M. A. (2015). Reduced graphene oxide induces transient blood-brain barrier opening: an in vivo study. *Journal of nanobiotechnology*, 13, 1-13.

Neha, B., Ganesh, B., & Preeti, K. (2013). Drug delivery to the brain using polymeric nanoparticles: a review. *International Journal of Pharmaceutical and Life Sciences*, 2(3), 107-132.

Ngowi, E. E., Wang, Y. Z., Qian, L., Helmy, Y. A. S. H., Anyomi, B., Li, T., ... & Ji, X. Y. (2021). The application of nanotechnology for the diagnosis and treatment of brain diseases and disorders. *Frontiers in Bioengineering and Biotechnology*, 9, 629832.

Nguyen, T. T., Nguyen, T. T. D., Vo, T. K., Nguyen, M. K., Van Vo, T., & Van Vo, G. (2021). Nanotechnology-based drug delivery for central nervous system disorders. *Biomedicine & Pharmacotherapy*, 143, 112117.

Pakhira, B., Ghosh, M., Allam, A., & Sarkar, S. (2016). Carbon nano onions cross the blood brain barrier. *RSC advances*, 6(35), 29779-29782.

Pardridge, W. M. (1998). CNS drug design based on principles of blood-brain barrier transport. *Journal of neurochemistry*, 70(5), 1781-1792.

Pardridge, W. M. (1998). CNS drug design based on principles of blood-brain barrier transport. *Journal of neurochemistry*, 70(5), 1781-1792.

Pardridge, W. M. (1999). Blood-brain barrier biology and methodology. *Journal of neurovirology*, 5(6), 556-569.

Pereira, C. D., Martins, F., Wiltfang, J., da Cruz e Silva, O. A., & Rebelo, S. (2017). ABC transporters are key players in Alzheimer's disease. *Journal of Alzheimer's Disease*, 61(2), 463-485.

Pisani, M. J., Wheate, N. J., Keene, F. R., Aldrich-Wright, J. R., & Collins, J. G. (2009). Anionic PAMAM dendrimers as drug delivery vehicles for transition metal-based anticancer drugs. *Journal of inorganic biochemistry*, 103(3), 373-380.

Plonska-Brzezinska, M. E. (2019). Carbon nano-onions: A review of recent progress in synthesis and applications. *ChemNanoMat*, 5, 568-580.

Quan, D., Obici, L., Berk, J. L., Ando, Y., Aldinc, E., White, M. T., & Adams, D. (2023). Impact of baseline polyneuropathy severity on patisiran treatment outcomes in the APOLLO trial. *Amyloid*, 30(1), 49-58.

Rhaman, M. M., Islam, M. R., Akash, S., Mim, M., Noor Alam, M., Nepovimova, E., ... & Sharma, R. (2022). Exploring the role of nanomedicines for the therapeutic approach of central nervous system dysfunction: at a glance. *Frontiers in Cell and Developmental Biology*, 10, 989471.

Ripp, S., & Henry, T. B. (2011). Biotechnology and nanotechnology risk assessment: minding and managing the potential threats around us. (*No Title*).

Roney, C., Kulkarni, P., Arora, V., Antich, P., Bonte, F., Wu, A., ... & Aminabhavi, T. M. (2005). Targeted nanoparticles for drug delivery through the blood-brain barrier for Alzheimer's disease. *Journal of controlled release*, 108(2-3), 193-214.

Saleh, A., Schroeter, M., Ringelstein, A., Hartung, H. P., Siebler, M., Mödder, U., & Jander, S. (2007). Iron oxide particle-enhanced MRI suggests variability of brain inflammation at early stages after ischemic stroke. *Stroke*, 38(10), 2733-2737.

Saralkar, P., Arsiwala, T., & Geldenhuys, W. J. (2020). Nanoparticle formulation and in vitro efficacy testing of the mitoNEET ligand NL-1 for drug delivery in a brain endothelial model of ischemic reperfusion-injury. *International journal of pharmaceutics*, 578, 119090.

Sharma, N., Zahoor, I., Sachdeva, M., Subramaniyan, V., Fuloria, S., Fuloria, N. K., ... & Singh, S. (2021). Deciphering the role of nanoparticles for management of bacterial meningitis: an update on recent studies. *Environmental Science and Pollution Research*, 1-18.

Sharma, U., Badyal, P. N., & Gupta, S. (2015). Polymeric nanoparticles drug delivery to brain: A review. *Int. J. Pharmacol*, 2(5), 60-69.

Siddiqi, K. S., & Husen, A. (2017). Recent advances in plant-mediated engineered gold nanoparticles and their application in biological system. *Journal of Trace Elements in Medicine and Biology*, 40, 10-23.

Siddiqi, K. S., Husen, A., Sohrab, S. S., & Yassin, M. O. (2018). Recent status of nanomaterial fabrication and their potential applications in neurological disease management. *Nanoscale*

research letters, 13, 1-17.

Soppimath, K. S., Aminabhavi, T. M., Kulkarni, A. R., & Rudzinski, W. E. (2001). Biodegradable polymeric nanoparticles as drug delivery devices. *Journal of controlled release*, 70(1-2), 1-20.

Sovey, N., Abdolahi, M., Djalali, M., Hatami, M., Tafakhori, A., Sarraf, P., & Honarvar, N. M. (2017). The combined effects of ω -3 fatty acids and nano-curcumin supplementation on intercellular adhesion molecule-1 (ICAM-1) gene expression and serum levels in migraine patients. *CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders)*, 16(10), 1120-1126.

Sozio, P., Fiorito, J., Di Giacomo, V., Di Stefano, A., Marinelli, L., Cacciatore, I., ... & Marrazzo, A. (2015). Haloperidol metabolite II prodrug: asymmetric synthesis and biological evaluation on rat C6 glioma cells. *European Journal of Medicinal Chemistry*, 90, 1-9.

Stenehjem, D. D., Hartz, A. M., Bauer, B., & Anderson, G. W. (2009). Novel and emerging strategies in drug delivery for overcoming the blood-brain barrier. *Future medicinal chemistry*, 1(9), 1623-1641.

Sun, M. C., Xu, X. L., Lou, X. F., & Du, Y. Z. (2020). Recent progress and future directions: the nano-drug delivery system for the treatment of vitiligo. *International Journal of Nanomedicine*, 3267-3279.

Tang, X., Liang, Y., Zhu, Y., Xie, C., Yao, A., Chen, L., ... & Hou, W. (2015). Anti-transferrin receptor-modified amphotericin B-loaded PLA-PEG nanoparticles cure Candidal meningitis and reduce drug toxicity. *International journal of nanomedicine*, 6227-6241.

Tunkel, A. R., & Scheld, W. M. (1993). Pathogenesis and pathophysiology of bacterial meningitis. *Clinical Microbiology Reviews*, 6(2), 118-136.

Tupone, M. G., Panella, G., d'Angelo, M., Castelli, V., Caioni, G., Catanesi, M., ... & Cimini, A. (2021). An update on graphene-based nanomaterials for neural growth and central nervous system regeneration. *International Journal of Molecular Sciences*, 22(23), 13047.

van Assema, D. M., Lubberink, M., Bauer, M., van der Flier, W. M., Schuit, R. C., Windhorst, A. D., ... & van Berckel,

B. N. (2012). Blood-brain barrier P-glycoprotein function in Alzheimer's disease. *Brain*, 135(1), 181-189.

Vibe, C. B., Fenaroli, F., Pires, D., Wilson, S. R., Bogoeva, V., Kalluru, R., ... & Hildahl, J. (2016). Thioridazine in PLGA nanoparticles reduces toxicity and improves rifampicin therapy against mycobacterial infection in zebrafish. *Nanotoxicology*, 10(6), 680-688.

Wang, J., Wang, H., Mo, X., & Wang, H. (2020). Reduced graphene oxide-encapsulated microfiber patterns enable controllable formation of neuronal-like networks. *Advanced Materials*, 32(40), 2004555.

Weil, A. G., Wang, A. C., Westwick, H. J., Ibrahim, G. M., Ariani, R. T., Crevier, L., ... & Fallah, A. (2017). Survival in pediatric medulloblastoma: a population-based observational study to improve prognostication. *Journal of neuro-oncology*, 132, 99-107.

Wick, P., Louw-Gaume, A. E., Kucki, M., Krug, H. F., Kostarelos, K., Fadeel, B., ... & Bianco, A. (2014). Classification framework for graphene-based materials. *Angewandte Chemie International Edition*, 53(30), pp-7714.

Wilhelm, I., & Krizbai, I. A. (2014). In vitro models of the blood-brain barrier for the study of drug delivery to the brain. *Molecular pharmaceutics*, 11(7), 1949-1963.

Wilson, B. (2009). Brain targeting PBCA nanoparticles and the blood-brain barrier. *Nanomedicine*, 4(5), 499-502.

Woehrl, B., Klein, M., Grandgirard, D., Koedel, U., & Leib, S. (2011). Bacterial meningitis: current therapy and possible future treatment options. *Expert review of anti-infective therapy*, 9(11), 1053-1065.

Wong, B. S., Yoong, S. L., Jagusiak, A., Panczyk, T., Ho, H. K., Ang, W. H., & Pastorin, G. (2013). Carbon nanotubes for delivery of small molecule drugs. *Advanced drug delivery reviews*, 65(15), 1964-2015.

Wu, H., Huang, Q., & Tan, Y. (2019). Carbon nanomaterials for biomedical applications. In *Carbon Nanomaterials: Modeling, Design, and Applications* (pp. 255-293). CRC Press.

Zhang, X., Goel, V., Attarwala, H., Sweetser, M. T., Clausen, V. A., & Robbie, G. J. (2020). Patisiran pharmacokinetics, pharmacodynamics, and exposure-response analyses in the phase 3 APOLLO trial in patients with hereditary transthyretin-

mediated (hATTR) amyloidosis. *The Journal of Clinical Pharmacology*, 60(1), 37-49.

Zhen, Z., & Zhu, H. (2018). Structure and properties of graphene. In *Graphene* (pp. 1-12). Academic Press.