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NANOPARTICLES FOR BRAIN DISEASE: TRANSLATIONAL FAILURES, BLOOD-BRAIN BARRIER HETEROGENEITY, AND PRECISION DESIGN CONSTRAINTS

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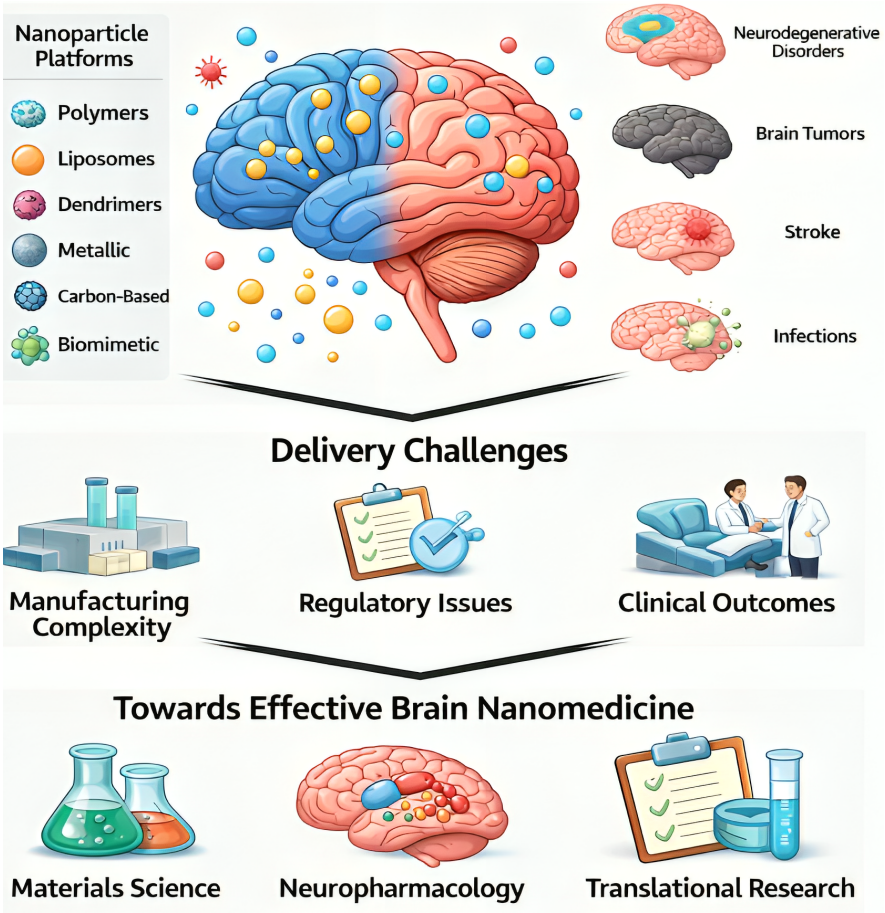
GRAPHICAL ABSTRACT



ABSTRACT

Brain-linked pathologies such as neurodegenerative diseases, malignant brain tumors, cerebrovascular and infectious neuropathologies remain difficult to diagnose and treat because of the restrictive and disease-dependent nature of biological barriers in the central nervous system. Although nanotechnology has achieved considerable preclinical success, the clinical implementation of nanoparticle-based brain treatments has been inconsistent, and a significant gap exists between experimental models and clinical reality. Nanoparticle strategies to overcome delivery barriers are critically analyzed with particular emphasis on theranostic systems and emerging biomimetic approaches. In addition to categorizing nanoparticles by class, we incorporate blood-brain barrier (BBB) structural and functional heterogeneity

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along with post-BBB transport constraints, including interstitial diffusion, cellular uptake variability, and intracellular trafficking, together with nanoparticle physicochemical design parameters such as size, surface charge, and functionalization, to explain why delivery outcomes are disease- and stage-dependent. Major nanoparticle platforms, including polymeric, liposomal, dendrimeric, metallic, carbon-based, and biomimetic systems, are being considered for Alzheimer's disease, Parkinson's disease, glioblastoma, stroke, and infectious brain pathologies. Integration of recent preclinical findings with emerging clinical trial evidence indicates that immune clearance, pharmacokinetic variability, limited tissue distribution, manufacturing complexity, and regulatory challenges are key contributors to translational failure. To address the trade-offs between multifunctional complexity and clinical feasibility, a disease-informed and regulation-aware framework is proposed to guide future nanoparticle development. Advancing brain nanomedicine will require coordinated progress across materials science, neuropharmacology, and translational research to move from proof of concept toward effective patient therapies.

Keywords: Nanoparticles; blood-brain barrier; brain-related diseases; nanomedicine; targeted drug delivery; theranostics; biomimetic nanoparticles; clinical translation

Purpose, Rationale, and Limitations

Despite major advances in nanotechnology, most brain-targeted nanomedicines fail during clinical translation. This high attrition rate largely stems from a "one-size-fits-all" design strategy that fails to account for the physiological heterogeneity of the BBB across diseases and patient populations.

This review aims to bridge the gap between preclinical success and clinical failure. We examine the physicochemical constraints — including size, surface charge, and surface chemistry — that govern BBB transport and post-BBB distribution, and we propose a disease-sensitive nanoparticle design framework that integrates regulatory and manufacturing considerations early in development.

We primarily focus on polymeric, liposomal, metallic, and biomimetic nanoparticle systems. Viral vectors, surgical implants, and device-based delivery approaches are not discussed in detail. In addition, psychiatric disorders in which BBB integrity is largely preserved are beyond the scope of this analysis.

Introduction

Neurodegenerative disorders, malignant brain tumors, cerebrovascular and infectious neuropathologies are brain-related and cause a significant and increasing global health burden. Alzheimer's disease (AD), Parkinson's disease (PD), glioblastoma multiforme (GBM), stroke, and central nervous system (CNS) infections have great morbidity, mortality, and long-term disability, whereas therapeutic success has not yet been achieved. The key factor contributing to this translational stagnation is that most systemically administered drugs at high doses cannot reach therapeutic concentrations in the brain [46, 84]. The blood-brain barrier (BBB), an extremely selective neurovascular barrier, is essential for preserving CNS homeostasis but also a significant impediment to the therapeutic and diagnostic delivery of agents [84, 33, 64].

The BBB consists of microvascular endothelial cells in the brain that are closely interconnected by pericytes, astrocytic end-feet, and the basement membrane, all of which together form the neurovascular unit [84, 33]. In addition to tight junctions, the BBB is also characterized by active efflux transporters, such as P-glycoprotein and breast cancer resistance protein, which further limit the accumulation of xenobiotics and macromolecular therapeutic agents in the brain [64, 12]. Notably, the BBB is not a fixed anatomical structure. It is permeable, expresses transporters, and exhibits inflammatory properties, which differ significantly depending on disease type, disease stage, aging, and systemic physiological endowments [64, 35]. Transient events like a stroke (or a high-grade brain tumor) can result in local focal BBB dysfunction, but long-term neurodegenerative conditions do not (particularly in the midbrain). This heterogeneity is vital to therapeutic delivery outcomes and causes significant interpatient variability [35].

Nanotechnology has emerged as a promising solution to overcome BBB-induced delivery constraints. Nanoparticles exhibit tunable physicochemical properties, such as nanoscale size, adjustable surface charge and chemistry, and high drug-loading capacity, which enable them to interact with endogenous BBB transport mechanisms, including receptor-mediated, adsorptive-mediated, and carrier-mediated

transcytosis [21, 37, 71, 17, 24]. Over the last 10 years, diverse nanoparticle platforms have been examined for brain-targeted drug delivery, brain imaging, and theranostic applications, including polymeric nanoparticles, liposomes, dendrimers, metallic nanoparticles, carbon-based systems, and biomimetic constructs [1, 2, 23, 27, 37]. The major transport pathways exploited by nanoparticles to traverse the BBB are schematically summarized in Figure 1.

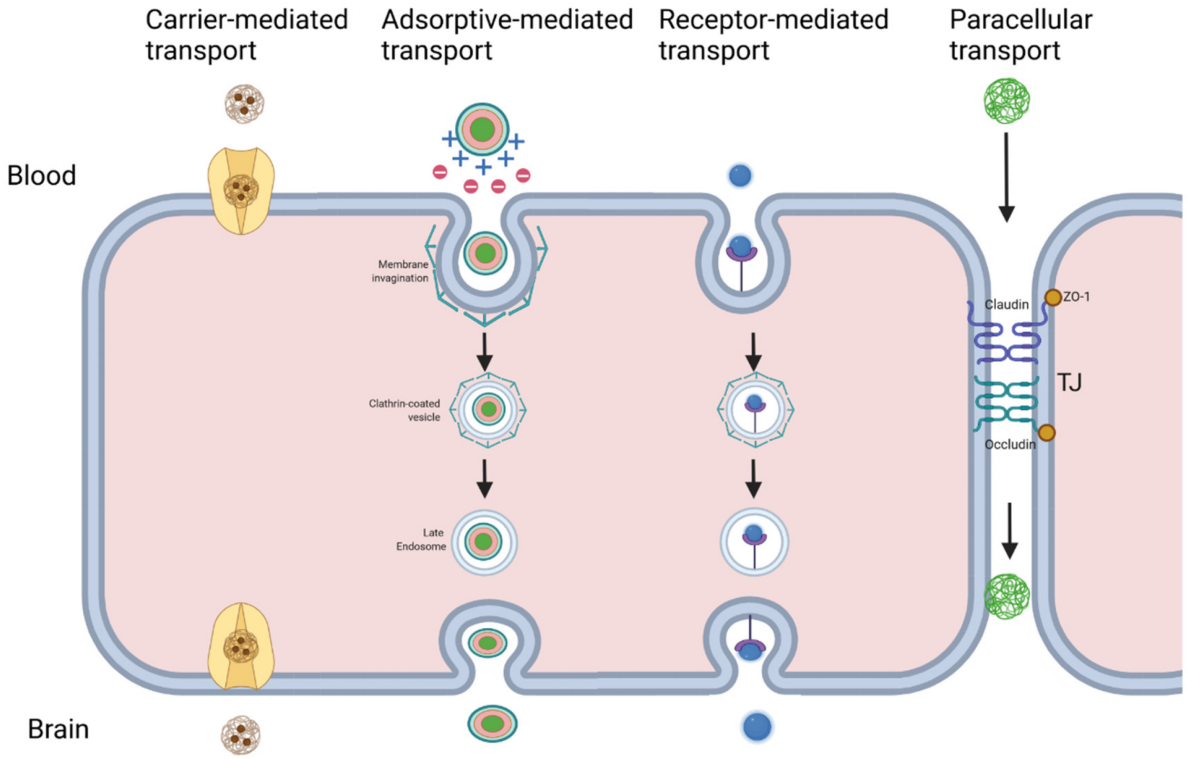

Figure 1. Nanoparticles may traverse the blood-brain barrier via carrier-mediated transport, adsorptive-mediated transcytosis, receptor-mediated transcytosis, and limited paracellular transport through tight junctions under specific pathological or experimental conditions. Vesicular internalization typically involves membrane invagination and trafficking through clathrin-coated pits or caveolae prior to release on the brain-facing side. While these mechanisms are widely exploited in preclinical nanomedicine studies, their efficiency and translational relevance remain highly variable and disease-dependent. Reproduced from [23] under the Creative Commons Attribution (CC-BY 4.0) license.

Although much brain nanoparticle therapy has been preclinically successful, clinical translation has been sparse and patchy. Numerous nanoparticle systems have demonstrated efficient penetration of the BBB and therapeutic efficacy in experimental models but have not yielded meaningful or reproducible outcomes in clinical settings [24, 73]. The reason for this translational gap is multifactorial. This is due to a lack of predictive value in animal and in vitro BBB models, combined with several other factors, such as rapid systemic clearance by the mononuclear phagocyte system, immunogenicity from surface modifications, and issues with large-scale manufacturing and regulatory approval [73, 22, 87, 14]. Consequently, BBB penetration alone has proven to be an incomplete design goal for clinically viable brain nanomedicines.

Some recent reviews offer insights into nanoparticle engineering for brain delivery, including classifications of materials, disease-targeted applications, and stimuli-responsive or organelle-targeted delivery systems [27, 36, 19, 1]. Although these contributions have improved mechanistic understanding, most are overly descriptive or focus on maximal functional complexity without adequately considering clinical feasibility, regulatory limitations, or the drivers of recurrent translational failure. In addition, few reviews directly integrate BBB heterogeneity, nanoparticle design trade-offs, and disease-

specific therapeutic needs into a single framework suitable for real-world clinical conditions.

Unlike previous reviews, which mainly categorize nanoparticle systems or focus on isolated BBB-crossing mechanisms, this review integrates BBB heterogeneity driven by disease, nanoparticle physicochemical design trade-offs, and translational viability within a single analytical framework. This work shifts the focus of nanomedicine design toward disease- and regulation-sensitive, scalable clinical nanoparticle systems, rather than further maximizing BBB permeability, given the critical scrutiny of the causes of failure in most nanoparticle structures in clinical translation despite their excellent preclinical responses. A precision nanomedicine framework that integrates considerations of BBB structure and nanoparticle transport is shown in Figure 2. Unlike previous reviews that primarily describe BBB-crossing mechanisms, this review emphasizes why BBB penetration alone has not led to clinical success. We integrate post-BBB transport barriers, disease-specific brain microenvironments, and translational constraints, including pharmacokinetics, immune clearance, and manufacturability, to provide a clinically-oriented design perspective.

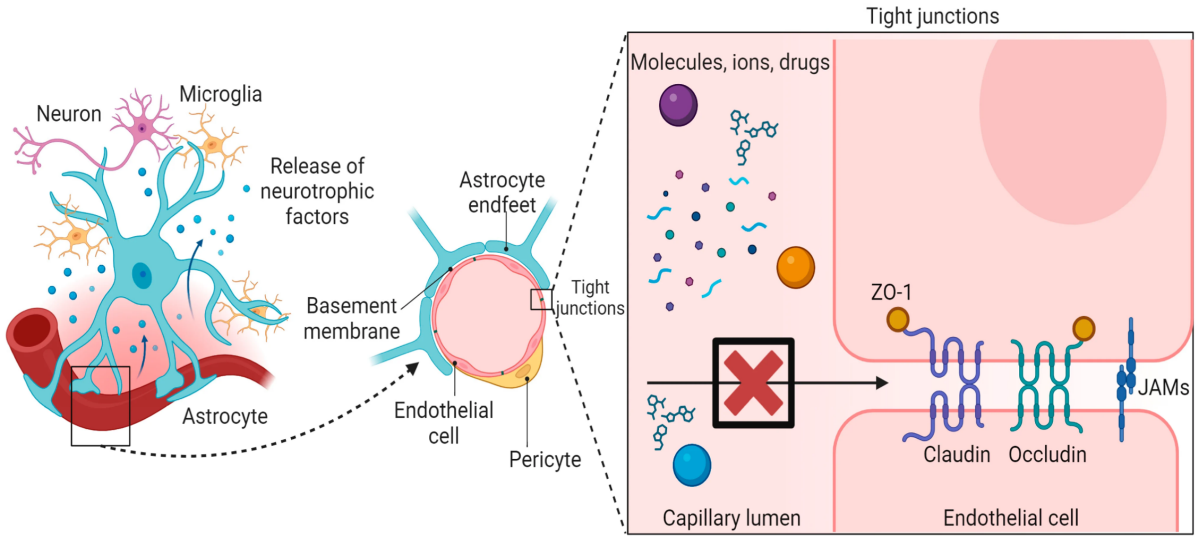

Figure 2. *The blood-brain barrier (BBB) is formed by brain microvascular endothelial cells, the vascular basement membrane, pericytes, and astrocyte end-feet, together constituting the neurovascular unit. Tight junctions between endothelial cells—composed of claudins, occludin, junctional adhesion molecules, and cytoplasmic adaptor proteins such as zonula occludens-1 (ZO-1)—severely restrict paracellular transport of most molecules, ions, and drugs. These structural features impose fundamental constraints on nanoparticle and drug delivery and contribute to disease- and context-dependent variability in brain targeting. Reproduced [4] under the Creative Commons Attribution (CC-BY 4.0) license*

DISCUSSION

The blood-brain barrier and its implications for drug delivery

Structure and Functional Dynamics of the Blood-Brain Barrier

The BBB is a well-defined neurovascular barrier that manages the exchange of molecules between the CNS and systemic circulation. It is enclosed by microvascular endothelial cells of the brain, interrelated by tight junctions, and surrounded by pericytes, astrocytic end-feet, and the basement membrane, which form the neurovascular unit [84, 33]. In addition to its physical appearance, the BBB expresses active efflux transporters, such as P-glycoprotein and breast cancer resistance protein, that limit the entry of xenobiotics and therapeutic substances into the brain [64, 12].

Notably, the BBB is a dynamic, disease-responsive mechanism rather than a fixed anatomical structure. It is more permeable, expresses more transporters, and is more inflammatory than in diseased, older, or more sys-

temic conditions [64, 35]. The localized disruption of the BBB can be caused by acute pathology (e.g., ischemic stroke and high-grade brain tumor). In contrast, chronic neurodegenerative conditions (e.g., Alzheimer's and Parkinson's diseases) are characteristic of the barrier's functional state (anatomically intact but functionally impaired). Such heterogeneity leads to substantial differences in drug and nanoparticle delivery outcomes across patients and diseases [35].

A substantial number of delivery strategies are based on simplified assumptions of homogeneous BBB permeability and optimized using experimental models that do not reflect the complexity of the human BBB [22, 51, 73]. This frequently leads to discrepancies or inadequate brain accumulation in clinical settings, even when BBB permeability is poor or efficient in preclinical studies. These findings reveal that the sole predictor of successful therapy is its penetration, which is achieved only when integrated with disease-specific BBB dynamics and patient heterogeneity [24, 73, 87].

Challenges in Treating Brain Diseases

Treatment of brain-related illnesses is not only difficult because of the restrictive nature of the BBB, but also because neurological disorders are biologically heterogeneous. Fewer than 5 percent of small-molecule drugs and fewer than 0.1 percent of macromolecular therapeutics reach pharmacologically relevant levels in the brain following systemic administration [9, 24, 64].

In neuro-oncology, effective drug dosing may only be achieved using high systemic doses, which causes severe off-target toxicities, while BBB disruption in tumors is still spatially heterogeneous and unpredictable [23]. Conversely, most neurodegenerative diseases, such as AD and PD, leave the BBB intact to a large extent, requiring long-term and repeated treatment with the concern of toxicity in the long run and accumulation of toxicity [35].

The schedules of the diseases also make the treatment more complex since the acute conditions like stroke require immediate response, whereas the neurodegenerative ones need to be delivered over the years. Invasive delivery techniques can be used to bypass the BBB; however, they pose a considerable risk, limiting their use in chronic treatment [23, 49]. These limitations underscore why BBB penetration alone is not sufficient to achieve clinical success.

Nanoparticle Approaches for Blood-Brain Barrier Penetration

Strategies to overcome the BBB using nanoparticles rely primarily on either developing endogenous transport routes or temporarily altering the barrier's permeability. These are receptor-mediated and adsorptive-mediated transcytosis, carrier-mediated transport, passive accumulation in areas of BBB disruption, and externally assisted delivery methods (Table 2). Despite evidence that most of these strategies improve brain uptake in experimental models, their clinical behavior is inconsistent and context-dependent [21, 37, 71, 17, 24].

Receptor-mediated transcytosis provides greater specificity but is limited by receptor saturation, competition with endogenous ligands, and interpatient variation in receptor expression, all of which limit delivery efficacy at true clinical doses [37]. Adsorptive-mediated transcytosis relies on nonspecific electrostatic interactions and is often associated with off-target uptake, rapid clearance, and immunogenicity [71]. Carrier-mediated transport is limited by transporter capacity and substrate competition, which restricts its use to small systems or those with only minimal modifications [17, 24].

BBB disruption-induced passive targeting, or the increased permeability and retention effect, is mostly limited to high-grade brain tumors and acute cerebrovascular diseases and is unreliable due to high spatial heterogeneity [23, 71]. Strategies aided externally, e.g., focused ultrasound, can transiently increase BBB permeability, although they raise safety, reproducibility, and clinical applicability issues, especially in chronic neurological diseases [90].

In general, none of the BBB penetration methods provides universal, long-lasting delivery to the brain. The maximality of BBB interaction can define clinical success, but the balance of delivery efficiency, safety, pharmacokinetics, and scalability determines success. Repeated translational failures are due to the continued use of single-mechanism optimization, underscoring the need for integrative, disease-aware delivery approaches.

Limitations of Current BBB Models and Translational Challenges

Although nanoparticle-based brain delivery systems exhibit attractive preclinical results, most have not been translated into clinical trials, largely because current BBB models are poorly predictive. The BBB systems of rodents differ significantly from the human BBB in transporter expression, tight junction arrangement, and immune interactions, often leading to overestimation of nanoparticle permeability and therapeutic effectiveness [72].

In vitro models of the BBB provide mechanistic insights; however, they are insufficient to recreate the complexity of the human microvascular blood vessel as a whole. Physiological shear stress, infection cell traffic, and disease-specific changes in the BBB are critical features that are either missing or simplified and thus cannot be forecast in vivo [51, 22]. As a result, nanoparticle formulations optimized using such systems often exhibit non-uniform brain accumulation during clinical trials.

Other translational barriers arise from poor pharmacokinetics and biodistribution. After systemic administration, a large fraction of the nanoparticles is rapidly removed by the mononuclear phagocyte system, leading to preponderant accumulation in the liver and spleen rather than in the brain. Multiple dosing may also increase immune activation, making it concerning that its effects may be long-lasting and unsafe [55, 91].

Stability and production are also more difficult due to complex architectures or large-scale surface functionalization. An example is nanoparticles that are batch-to-batch variable during scale-up, where small changes in size or surface chemistry can significantly alter biodistribution and efficacy. These aspects make it difficult to obtain regulatory approval and have even led to subpar clinical outcomes for numerous experimental nanomedicines [87, 43].

NANOPARTICLE DESIGN PRINCIPLES GOVERNING BRAIN TARGETING AND CLINICAL TRANSLATION

Physicochemical Determinants of Brain-Targeted Nanoparticles

The penetration of nanoparticles into brain tissue, the BBB, and the systemic circulation is determined by trade-offs among delivery efficiency, pharmacokinetics, immune compatibility, and manufacturability, rather than the optimization of a specific physicochemical parameter [21, 24, 48, 72, 85, 87]. Designs that focus solely on BBB penetration often fail to translate clinically due to poor biodistribution and safety concerns.

The size of nanoparticles and their surface charge have opposing effects on circulation and BBB transport. Smaller particles can increase endothelial uptake but are quickly eliminated, whereas larger particles have a longer circulatory lifespan but are sterically restricted in transcytosis [21, 72, 85]. In the same vein, cationic nanoparticles enhance cellular engagement at the expense of decreased BBB engagement, whereas neutral or weakly anionic systems prefer circulation at the expense of reduced circulation [71, 24, 87].

Stability, degradation, and drug release are controlled by surface chemistry. Even though premature cargo leakage and inconsistent degradation can undermine efficacy, biodegradable polymers or lipid-based systems are usually preferred [87, 14]. Surface functionalization-PEGylation or ligand conjugation can extend the circulation or increase targeting, but have the complication of manufacturing variability by batch, making batches more difficult to regulate and can present regulatory problems [87, 14, 45, 91]. Taken together, the simplicity and reproducibility of nanoparticle designs have greater translational potential than high-complexity multifunctional systems [24, 87, 91].

Surface Engineering and Functionalization Strategies

Depending on the desired clinical application and translational limitations, surface functionalization plans are chosen. PEGylation has extensive applications in prolonging circulation in the phagocytic system and reducing immunogenicity, but excessive cell-surface shielding interferes with cellular internalization and receptor-mediated BBB translocation [45]. Ligand conjugation allows selective engagement with BBB receptors or disease-relevant markers; however, targeting ligand specificity is often limited by receptor saturation and disease-specific interpatient variability [21]. Surface modification with diagnostic imaging or real-time tracking using magnetic or fluorescent

moieties facilitates surface biointeractions, despite their limited impact on therapeutic accumulation [43]. More sophisticated biomimetic methods, such as coating nanoparticles with red blood cell or platelet membranes, increase immune evasion and half-life but pose serious challenges in fabrication, scalability, and control [87].

TYPES OF NANOPARTICLES USED IN BRAIN-RELATED DISEASES

Table 1 summarizes the popular nanoparticle platforms for treating brain-related diseases, their main strengths, and translational shortcomings.

Polymeric Nanoparticles [11], [32], [61]

One of the most widely researched delivery systems in brain-targeted drug delivery is polymeric nanoparticles, since they are biodegradable and their regulation is well established. However, the negative impact of inconsistent accumulation in the brain, inconsistent therapeutic efficacy, and long-term administration has impeded clinical translation. The composition and degradation kinetics of polymers significantly affect drug release and biological fate.

Table 1. Comparison of major brain-related disease diagnosis and therapy platforms relying on nanoparticles.

Nanoparticle Type	Key Advantages	Translational Limitations	Applications
Polymeric (e.g., PLGA, Chitosan)	Biodegradable; high drug-loading capacity; sustained release; tunable degradation profiles [61], [69]	Inconsistent brain accumulation; acidic degradation by-products; rapid systemic clearance [22], [69]	Tau-targeting strategies for Alzheimer's disease [54] ; siRNA delivery for glioblastoma multiforme (GBM) [11]
Liposomes	High biocompatibility; capable of encapsulating both hydrophilic and lipophilic drugs; low immunogenicity [60]	Physical instability; premature drug leakage; rapid clearance without surface modification[89]	Doxorubicin delivery for GBM [95]; general central nervous system (CNS) drug delivery strategies [89]
Dendrimers	Monodisperse structure; precise molecular architecture; abundant surface functional groups for targeting [8], [34]	Dose-dependent cytotoxicity; concerns regarding long-term safety and accumulation [34]	Delivery of therapeutics for cerebral palsy and excitotoxicity [88]; CNS drug delivery [8]
Metallic (e.g., Gold, Iron Oxide)	Tunable optical and magnetic properties; strong theranostic potential (imaging + therapy) [76]	Potential toxicity due to accumulation; poor biodegradability [26], [94]	Photothermal ablation for GBM [5]; Magnetic resonance imaging contrast enhancement for brain tumors [76]
Carbon-Based (e.g., Carbon Nanotubes, Graphene)	High surface area; excellent electrical conductivity; efficient gene/drug loading via π–π interactions [29], [93]	Induction of oxidative stress; inflammatory responses; long-term biopersistence [94]	Neural interfacing for regeneration [62]; drug delivery in Parkinson's disease [42]
Biomimetic (e.g., Cell Membrane-Coated Nanoparticles)	Immune evasion; prolonged systemic circulation; enhanced targeting of inflamed or diseased brain regions [82], [92]	Complex fabrication processes; scalability challenges; regulatory uncertainty [22], [91]	Red blood cell membrane-coated nanoparticles for BBB crossing in stroke [30]; leukocyte membrane-coated systems for GBM targeting [92]

The systems made from PLGA can provide sustained release, though they can exhibit early drug release and acidic degradation by-products, whereas chitosan-based nanoparticles can interact with the BBB at the expense of high immune recognition and rapid clearance. It is worth noting that polymeric systems that are effective in acute disease models do not work in chronic neurological disease models, suggesting that their application is mostly limited to short-term, localized, or even adjunctive therapy rather than long-term systemic therapy.

Liposomes [59], [60], [89]

Liposomes are also the most mature nanoparticle platforms as they possess a phospholipid bilayer structure, high biocompatibility with their bioproducts, and well-developed manufacturing guidelines. In brain cancer, liposomal chemotherapeutics have been shown to accumulate more effectively in tumors and reduce systemic toxicity, and antibody-conjugated liposomes have also been reported to accumulate more effectively and have the potential to serve as targeted imaging and delivery agents in AD. Despite these strengths, liposomal systems are limited by physical instability, premature drug release, and rapid clearance when not surface-attached. As a result, liposomes are preferable for oncological, intrathecal, or short-term use rather than for chronic neurodegenerative disorders, which are widely used.

Dendrimers [8], [34], [88]

Dendrimers are highly branched, monodisperse nanostructures that enable surface functionalization and accurate drug loading. They are selectively accumulated in activated microglia and inflammatory brain regions in the neuroinflammatory and rare metabolic disorders and can be used in neurology. Nonetheless, the range of translational advancement is limited by dose-dependent cytotoxicity and by still-unaddressed sustainability issues, especially in higher generations. Consequently, dendrimer-based systems are limited to a niche or early-stage use, with controlled, small-dose administration.

Metallic Nanoparticles [5], [26], [56]

Nanoparticles made of metals, especially gold and iron oxides, can be used because of their unique optical and magnetic properties, which are beneficial for treating brain diseases. Gold nanoparticles are useful for local tumor ablation via photothermal therapy, and iron oxide nanoparticles improve magnetic resonance imaging and cell tracing. Despite these benefits, concerns about biodegradability, long-term accumulation, and even toxicity have limited their use as long-term therapeutic delivery systems. As such, metallic nanoparticles have been even more successful in translational diagnostic/monitoring applications compared to sustained drug delivery.

Carbon-Based Nanoparticles [29], [62], [93]

Carbon nanomaterials (such as carbon nanotubes and graphene oxide) have high surface areas and are electrical conductors, which enables manipulation in the fields of neural interfacing and drug delivery in experimental settings. Nonetheless, induction of oxidative stress, inflammation, and long-term biopersistence is one of the greatest setbacks to clinical translation. Variability in surface functionalization and synthesis only complicates safety assessment and reproducibility. It is therefore found that carbon-based nanoparticles are, at best, still an exploratory research tool and not yet a common practice in therapy.

Biomimetic Nanoparticles [6], [82], [92]

Cell membrane-coated systems and biomimetic nanoparticles can exploit endogenous biological properties to enhance immune evasion and prolong circulation time. The membrane coatings on red blood cells and leukocytes facilitate delivery to inflamed or diseased areas of the brain. Despite high conceptual efficacy, challenges in clinical translation stem from sophisticated production, scaling issues, variability, and regulatory uncertainty. Mass use will require reduced designs and standardized manufacturing approaches.

MECHANISMS OF NANOPARTICLE-MEDIATED DRUG DELIVERY TO THE BRAIN

Table 2 presents the key mechanisms by which nanoparticles cross the BBB, along with their strengths and weaknesses.

There are several pathways for nanoparticle-mediated transport across the BBB, each with unique pros and cons. Passive targeting can be used to exploit the propensity for localized BBB disruption in disease tissues; for example, brain tumors frequently have leaky vasculature, which permits nanoparticle aggregation via enhanced permeability and retention. Neverthe-

less, this process is not very effective in neurodegenerative diseases, where the BBB is not structurally damaged [14]. Active targeting relies on the interaction between ligands and receptors, whereby nanoparticles functionalized with transferrin, lactoferrin, apolipoproteins, or integrin-binding peptides bind to endothelial or tumor-associated receptors and undergo receptor-mediated transcytosis [21, 25]. Conversely, stimuli-responsive nanoparticles do not control BBB transport but primarily regulate cargo release in response to pathological conditions such as low pH, reactive oxygen species, or physical stimuli, thereby releasing the drug in a spatially and temporally controlled manner [19].

Table 2. Mechanisms of nanoparticle transport across the blood-brain barrier

Mechanism	Description	Advantages	Limitations
Receptor-Mediated Transcytosis	Ligand-functionalized nanoparticles (e.g., transferrin, insulin) bind endothelial receptors and undergo vesicular transport across the blood-brain barrier (BBB) [21]	High specificity; controlled and efficient uptake [21], [37]	Receptor saturation; interpatient variability in receptor expression [21], [64]
Adsorptive-Mediated Transcytosis	Electrostatic interaction between positively charged nanoparticles and negatively charged endothelial membranes [17]	Simple strategy; enhanced endothelial adhesion [17], [37]	Nonspecific uptake; off-target accumulation; potential immunogenicity [71]
Carrier-Mediated Transport	Nanoparticles mimic endogenous substrates (e.g., glucose, amino acids) to exploit membrane transporters [12]	Utilizes natural BBB transport pathways [12], [17]	Limited by transporter size and capacity; competition with endogenous substrates [12]
Passive Targeting	Accumulation of nanoparticles through leaky tumor vasculature and impaired lymphatic drainage [47]	No surface modification required [47], [80]	Highly heterogeneous; ineffective for intact BBB (e.g., Alzheimer's disease) [47]
Stimuli-Responsive Release	Nanoparticles release cargo in response to internal (pH, reactive oxygen species , enzymes) or external stimuli after BBB uptake [19]	Spatial and temporal control; reduced off-target toxicity [19]	Complex design; unpredictable in vivo responsiveness [19]
Externally Assisted Transport (e.g., Ultrasound)	Temporary BBB disruption using focused ultrasound or chemical agents to enhance permeability [13], [52]	Dramatically improves nanoparticle brain accumulation [13]	Risk of neurotoxicity; requires specialized equipment and precise control [52]

BLOOD-BRAIN-BARRIER TRANSPORT: INTERSTITIAL MOVEMENT AND CELLULAR UPTAKE

Crossing the BBB represents only the first step in successful brain drug delivery. After transcytosis, nanoparticles enter the brain parenchyma, where additional biological barriers critically influence therapeutic distribution and efficacy. Failure at this stage is increasingly recognized as a major reason why nanoparticles that appear successful in BBB models do not achieve meaningful outcomes in vivo [24, 73, 87].

The brain extracellular matrix (ECM) forms a dense, nanoporous environment composed of glycosaminoglycans, proteoglycans, and structural proteins that can significantly restrict the movement of nanoscale materials **[7]**. Unlike

many peripheral tissues, transport within the brain parenchyma is largely diffusion-driven, and nanoparticle size and surface properties strongly influence the extent of distribution from cerebral blood vessels [77]. Larger nanoparticles, in particular, often exhibit reduced mobility within extracellular matrices due to steric hindrance and interactions with matrix components, thereby limiting their penetration into neural tissue [10, 77].

In biological extracellular matrices more broadly, nanoparticle movement can be further limited by steric hindrance and adhesive interactions with matrix components, with surface chemistry playing a key role in determining mobility [10]. Hydrophilic coatings such as polyethylene glycol (PEG) reduce nonspecific interactions with biological components [45], whereas surfaces that promote biomolecular adsorption may experience localized retention and reduced tissue penetration [10]. These physicochemical constraints help explain why nanoparticles engineered for efficient BBB transport may still achieve limited distribution within neural tissue, restricting their therapeutic reach in diffuse neurodegenerative disorders.

Following interstitial transport, cellular uptake presents another major barrier. Neurons, astrocytes, microglia, and tumor cells differ substantially in endocytic capacity and receptor expression. Microglia and perivascular macrophages preferentially internalize nanoparticles, leading to immune sequestration rather than delivery to intended neuronal targets [39, 87]. Even when internalized by target cells, nanoparticles may remain trapped within endolysosomal compartments, preventing cytosolic drug release unless specific endosomal escape mechanisms are incorporated [53].

The relative importance of post-BBB transport barriers varies across neurological diseases. In neurodegenerative disorders such as Alzheimer's and Parkinson's diseases, where pathological targets are widely distributed, effective therapy requires broad distribution through the brain parenchyma; however, nanoparticle diffusion remains strongly constrained by the dense extracellular matrix, which limits tissue coverage even after successful BBB transcytosis [35, 77]. In contrast, brain tumors such as glioblastoma may exhibit focal disruption of the BBB, allowing nanoparticle entry. Still, abnormal extracellular matrix composition and structural heterogeneity of the tumor often lead to uneven intratumoral distribution and poor penetration into infiltrative tumor margins [23, 28, 69]. In acute cerebrovascular conditions such as ischemic stroke, transient edema, and BBB alterations, interstitial spacing and local transport properties may be temporarily altered. Still, these effects are highly variable in space and time, reducing the predictability of nanoparticle dispersion within affected tissue [30, 72]. These disease-dependent differences reinforce that post-BBB transport is not a uniform process and must be considered pathologically specific during nanoparticle design.

Therefore, effective brain nanomedicine design must integrate three sequential requirements: BBB transcytosis, efficient interstitial diffusion, and cell-specific uptake with intracellular drug release. Ignoring post-BBB transport leads to overestimation of therapeutic potential in preclinical models and contributes significantly to translational failure [24, 23, 35].

APPLICATIONS OF NANOPARTICLES IN SPECIFIC BRAIN DISEASES

Alzheimer's Disease [50], [54], [70], [80]

AD is a neurodegenerative disease caused by the aggregation of amyloid-beta, tau lesions, synaptic dysfunction, and neuroinflammation . Although there has been a great development in the treatments, the currently approved ones may only offer symptomatic relief without altering the progression of the disease, primarily because of ineffective delivery of the drugs to the affected brain areas and because of late intervention into the disease.

Nanoparticle-based approaches to disease modification have not achieved disease-modifying effects in AD, despite their extensive preclinical success. This not only indicates delivery constraints but also inherent biological limitations, such as the low correlation between cognitive improvement and amyloid reduction, coupled with a general tendency to intervene in the disease at an advanced stage.

Table 3. Nanoparticle-based strategies for major brain-related diseases

Disease	Therapeutic Objectives	Key Nanoparticle Strategies	Challenges
Alzheimer's Disease	Reduction of amyloid-β and tau pathology; neuroprotection; early-stage imaging and diagnosis [75]	Polymeric nanoparticles for curcumin/resveratrol delivery; liposomal anti-amyloid antibodies [31], [44]	Late clinical intervention; multifactorial disease mechanisms; lack of definitive disease-modifying therapies [36]
Parkinson's Disease	Dopamine replacement; antioxidant therapy; stem cell and neuronal tracking [40]	Chitosan-based nanoparticles for dopamine delivery; nanoenzymes; magnetic nanoparticles for imaging and tracking [40] [86]	Chronic disease progression; peripheral side effects; limited targeting specificity [40]
Glioblastoma Multiforme	Tumor ablation; gene silencing; enhancement of chemotherapy efficacy [15]	Liposomal doxorubicin; gold nanoparticles for photothermal therapy; polymeric nanoparticles for siRNA delivery [38], [95]	Extreme tumor heterogeneity; therapy resistance; variable BBB permeability [72], [78]
Stroke / Cerebrovascular Disorders	Thrombolysis; neuroprotection; reactive oxygen species scavenging [30]	Nanoparticle-encapsulated tissue plasminogen activator (tPA); cerium oxide antioxidant nanoparticles [30], [72]	Narrow therapeutic time window; blood-brain barrier (BBB) disruption variability; hemorrhagic risk [30]
Infectious Brain Diseases	Targeted antimicrobial delivery; inflammation reduction [79]	Chitosan-based nanoparticles for anti-tubercular therapy; nanoparticle-mediated antiviral delivery [17], [79]	Antimicrobial resistance; prolonged treatment duration; complex immune interactions [79]

Although nanoparticles have the potential of expanding brain exposure to therapeutic agents, they cannot correct multifactorial pathology or irreversible neuronal death. The nanoparticle-based approaches used for disease diagnosis or as adjuncts in the delivery of therapeutic agents in the treatment of the disease have a higher chance of succeeding as diagnostic tools or delivery systems, but not independently as disease-modifying agents in the treatment of the disease.

Parkinson's Disease [40], [41], [86]

PD is a progressive motor disorder caused by the deterioration of dopaminergic neurons in the substantia nigra and deposition of α-synuclein foci. Traditional regimens of pharmacological therapy led to a symptomatic effect but are restricted due to either low brain bioavailability, peripheral side effects, or decreases in efficacy with time.

Formulations involving nanoparticles have also been explored as improved methods for delivering dopamine, dopamine precursors, and neuroprotective factors into the brain. Nanoparticles made of chitosan have been shown to stimulate sustained dopamine release and bioavailability in experimental models, with nanoenzymes with antioxidant potential having been shown to reduce oxidative stress-related neuronal damage. Moreover, magnetic nanoparticles can be used to track transplanted stem cells, providing information on regenerative strategies in PD.

Although nanoparticle formulations enhance the biological activity of dopaminergic and neuroprotective compounds in animal models,

in human subjects, nanoparticles are only marginally effective in PD. The characteristic course of chronic diseases, the susceptibility of regions to neural damage, and interpersonal variations in the ability of the BBB to limit lasting therapeutic benefit. The development of strategies across most nanoparticle deals can be seen as symptomatic deficits rather than underlying neurodegeneration. In this regard, nanoparticle platforms in PD nowadays achieve optimal functionality as adjunctive delivery systems, and long-term safety and repeated-dose administration are significant translational constraints.

Glioblastoma Multiforme [58], [16], [18], [69]

The glioblastoma multiforme (GBM) is the most lethal primary tumor of the brain; it is rapidly proliferating, diffuse, and invasive, as well as having resistance against such conventional therapies as chemotherapy and radiotherapy. The presence of a robust or heterogeneously breached BBB significantly limits the effectiveness of systemically administered therapeutics.

The use of nanoparticles has increased the potential for treating glioblastoma by enhancing drug delivery and enabling gene- or energy-based therapies. Nevertheless, the clinical findings are limited by tumor heterogeneity, adaptation resistance, and heterogeneity in BBB permeability across space. The accumulation of nanoparticles may be confined to perivascular or necrotic areas, and infiltrative tumor margins may not be adequately addressed [16, 69, 81]. This is due to limitations, suggesting that nanoparticle-based therapies are most effective when combined with surgery and radiotherapy, but not as individual therapies.

Stroke and Cerebrovascular Disorders [30], [72]

The blocked circulation of cerebral blood causes ischemia, which is a form of stroke that causes cells to die rapidly, produces oxidative stress, and causes inflammation cascades. Although the therapy process is effective, therapeutic intervention within a limited period of time is required, and drug delivery systems are seriously challenged.

Nanoparticles are being investigated as a thrombolytic agent, a neuroprotective drug, and an antioxidant carrier. To prevent bleeding complications associated with aspirin administration, encapsulation of tissue plasminogen activator into nanoparticle systems has been examined to enable limited release. Hexafluorides of Cerium oxide nanoparticles, a type of catalytic scavenger of reactive oxygen species, have been shown to offer neuroprotection in experimental stroke models. Although it has shown positive outcomes, the nature of stroke pathology prevents progression to clinical translation due to its acute and time-sensitive characteristics. The limitations to the homogeneity of nanoparticle therapy delivery include delays in diagnosis, patient heterogeneity, and varying BBB disruption. Consequently, nanoparticle-based stroke technologies are still in their early stages of development and can be most useful in the context of fast diagnostic and targeted therapeutic systems.

Infectious Brain Diseases [3], [20], [66]

The infections of the CNS, such as neurotuberculosis, viral encephalitis, are also linked to high morbidity and mortality rates because of low penetration of antimicrobials through the BBB. Prolonged therapy courses and resistance to the drugs further complicate therapeutic management.

Nanoparticle-based delivery systems have been investigated to enhance the ability of antimicrobial agents to penetrate the brain, reduce systemic toxicity, and optimize therapeutic efficacy. Nanoparticles of anti-tubercular drugs that are carried by chitosan have been shown to increase CNS accumulation and improve clearance of malignant bacteria in preclinical models, whilst nanoparticle preparations of antiviral drugs have the potential to reduce viral burden in brain tissue. But translational development is hindered by differences in infection-related disruption of the BBB, immune-mediated pathology, and the long-term safety of nanoparticles for long-term treatment. These issues demonstrate the necessity of developing pathogen-specific delivery plans and of considering immunological interactions to apply them in clinical practice.

WHY HAVE MOST NANOPARTICLE-BASED BRAIN THERAPIES FAILED CLINICALLY?

Although much has been done with nanoparticles in preclinical research, comparatively limited therapeutic applications in brain-related

diseases have not been translated into clinical use. A key factor contributing to this concern in clinical translation is that preclinical models have very limited predictive capacity. Animal models do not necessarily reflect the complexity, heterogeneity, and chronic evolution of human neurological diseases and, as a result, overestimate therapeutic effectiveness. Moreover, disease-induced changes in the human BBB are highly variable, hindering consistent nanoparticle delivery across the entire patient population [79].

There is also the problem of pharmacokinetics and biodistribution that inhibits clinical success. Nanoparticles that exhibit effective BBB penetration in controlled test systems often undergo rapid clearance or off-target accumulation in vivo. Hepatic, splenic, and mononuclear phagocytic sequestration impairs brain delivery and, over the long term, can result in toxicity and accumulation [39].

The crucial impediments to translation are safety and immunogenicity. Surface alterations that improve targeting or circulation time can also have unintended effects, such as activating immune pathways and triggering complement activation, inflammation, or hypersensitivity reactions. These risks are increased in chronic neurological diseases and require extremely high levels of safety where prolonged administration is ongoing [55, 68, 94].

Complexity in manufacturing and regulatory uncertainty are also the main causes of clinical failure. Multifunctional nanoparticles with highly complex architectures are typically poorly scalable, and even minor changes in size, surface chemistry, or drug content can significantly affect biological behavior. Physicochemical characterization and uniform production procedures mandated by regulatory bodies are not met by most current experimental nanoparticle systems [22, 91].

In addition, even when nanoparticles successfully cross the BBB in experimental models, limited interstitial transport, heterogeneous cellular uptake, and inefficient intracellular drug release in the human brain further reduce therapeutic effectiveness. All these difficulties suggest that strong translation requires predictive, disease-relevant models, simpler and scalable nanoparticle designs, and the integration of regulatory aspects into development pipelines.

NANOPARTICLES FOR BRAIN IMAGING AND DIAGNOSTICS

Nanoparticles play an important role in the diagnostic imaging modalities such as magnetic resonance, optical, and nuclear imaging. Iron oxide nanoparticles generate a powerful magnetic field disturbance detectable by MRI, yielding high-contrast images of tumors, inflammatory lesions, and neural pathways. Ultra-small superparamagnetic iron oxide nanoparticles have been used to differentiate pathological tissue from healthy brain tissue with high accuracy [43], [56], [83].

Quantum dots have been used in optical imaging to achieve outstanding brightness and photostability for real-time visualization of neuronal structures, whereas gold nanoparticles in plasmonic imaging have been used to enhance contrast and map the tumor microenvironment. In positron emission tomography and single-photon emission computed tomography, targeted radionuclide-conjugated nanoparticles are used to image biomarkers of neurodegeneration or tumorigenesis, facilitating early disease detection and aiding disease monitoring [5, 67, 70]. Nanoparticles designed as diagnostic and imaging devices have demonstrated relatively high translational success compared to therapeutic platforms, owing to their clearly defined clinical utility and regulatory pathways [56, 83].

In more advanced applications, theragnostic nanoparticles combine diagnostic and therapeutic capabilities in a single system, enabling drug delivery and monitoring of treatment response; however, their development has been hindered by the increased complexity of their structures. This difference helps explain why nanoparticle-based imaging agents have achieved smoother clinical translation than therapeutic systems, which must overcome additional biological barriers such as deep-tissue penetration and intracellular drug delivery.

TOXICOLOGICAL AND SAFETY CONSIDERATIONS

Despite these advances, nanoparticles require extensive safety analysis before clinical application. Possible toxicities include oxidative stress, DNA damage, inflammation, and retention in non-target organs, such as the liver and spleen. Surgeons must be careful when modify-

ing the surfaces of metal nanoparticles, especially those containing toxic elements such as heavy metals. Biodegradable nanoparticles, such as poly(lactic-co-glycolic acid) systems, tend to be safer but must be considered for their degradation products and long-term effects.

Safe design principles are based on biocompatibility, controlled degradation, surface neutrality, and minimal immunogenicity. Regulatory organizations, such as the U.S. Food and Drug Administration, the European Medicines Agency, and the Nano Mission of India, have developed guidelines on the characterization of nanoparticles, toxicology, and clinical translation. For cross-study comparability and patient safety, standardized testing procedures remain required [63, 91, 94].

These safety uncertainties further slow clinical translation, particularly for chronic neurological disorders that would require repeated or long-term nanoparticle administration.

CLINICAL TRIALS AND TRANSLATIONAL PROGRESS

Nanoparticle-based systems for the clinical translation of brain-related diseases have not been studied extensively, and comparatively few platforms have progressed beyond early-phase studies. The first clinical activities have focused more on improving drug retention, increasing imaging sensitivity, and reducing systemic toxicity than on disease modification. Liposomal formulations are considered the most advanced nanoparticle form in medicine, and some products are approved or under investigation for CNS cancer and leptomeningeal diseases. Liposomal cytarabine, for example, has been shown to have a longer shelf life in cerebrospinal fluid and better therapeutic exposure in lymphoma meningitis [60].

Clinical success has been relatively high with nanoparticles developed for diagnostic imaging. Superparamagnetic iron oxide nanoparticles have also been considered as MRI contrast agents for brain tumors, neuroinflammation, and cell tracking, owing to their defined physicochemical characteristics and safety profiles. Conversely, multifunctional theranostic nanoparticles are largely still in the preclinical stage due to their greater complexity and regulatory hurdles [56, 83].

Polymeric nanoparticles loaded with chemotherapeutic agents, nucleic acids, or neuroprotective compounds have already undergone early clinical trials in brain tumors and neurodegenerative diseases, but a lack of consistent brain and interpatient differences in BBB accumulation, as well as dose optimization, has slowed their progress. There are other challenges associated with gene- and RNA-based nanoparticle therapies, including intracellular delivery efficiency, off-target effects, and long-term safety [79]. The more straightforward nanoparticle-based designs that lack well-illustrated mechanisms of action have typically progressed more quickly through regulatory procedures than multifunctional systems [91].

Despite extensive preclinical research on nanoparticle-mediated brain delivery, only a limited number of platforms have advanced to clinical evaluation. These studies provide important insights into how nanomedicine strategies are being translated into human clinical trials, including the types of nanoparticle systems used, the diseases targeted, and the clinical stages reached. Representative ongoing and completed interventional studies involving nanoparticle-based systems for CNS disorders are summarized in Table 4.

As shown in Table 4, clinical translation of nanoparticle systems in CNS disorders is currently concentrated in neuro-oncology, particularly glioblastoma and other malignant brain tumors, where poor prognosis and limited treatment options justify early-phase experimental approaches. In contrast, only a small number of exploratory trials have evaluated nanoparticle therapeutics in neurodegenerative diseases such as PD. Notably, despite several nanoparticle platforms reaching Phase 1 and Phase 2 clinical evaluation, no nanoparticle-based therapy has yet advanced to Phase 3 trials for CNS disorders. This highlights the substantial translational barriers that remain, including inconsistent therapeutic efficacy, variability in delivery within the human brain, limited patient populations, and high regulatory and financial thresholds for late-stage development. This imbalance between oncology and non-oncology applications underscores ongoing challenges in achieving safe, effective, and scalable nanoparticle delivery for chronic neurological disorders.

Table 4. Clinical trials of nanoparticle-based systems evaluated in patients with central nervous system disorders

Disease	Nanoparticle Platform	Phase	Enrollment	Status	Reference
Parkinson's Disease	CNM-Au8 gold nanocrystals	Phase 2	13	Completed	[96]
Diffuse Intrinsic Pontine Glioma (DIPG)	MTX110 panobinostat nanoparticle (CED)	Phase 1/2	7	Completed	[97]
Diffuse Midline Glioma (DMG)	MTX110 panobinostat nanoparticle (CED)	Phase 1	9	Completed	[98]
Recurrent Glioblastoma	EGFR(V)-EDV-Dox targeted nanocell (doxorubicin)	Phase 1	9	Completed	[99]
Multiple Brain Metastases	AGuIX gadolinium nanoparticles (NANO-RAD radiosensitization)	Phase 1	15	Completed	[100]
Brain Metastases (stereotactic RT ± AGuIX)	AGuIX gadolinium nanoparticles + stereotactic radiation	Phase 2	134	Recruiting/Ongoing	[101]

FUTURE TRENDS AND EMERGING TECHNOLOGIES

The principles of therapeutic complexity versus clinical practicability will guide the further development of nanoparticle-based methods for treating brain diseases. One development is the move towards simpler, modular nanoparticle designs that retain delivery performance while reducing structural complexity, thereby increasing reproducibility and regulatory friendliness.

Next-generation delivery systems should also make use of biomimetic and bioinspired nanoparticles. Immunoevasive nanoparticles, surface-decorated with endogenous cell membrane components or designed to resemble natural transport substrates, have a greater capacity to evade the host organism's immune system and avoid immune surveillance of their cancer-tumor target without undergoing violent surface-engineered adaptations that can elicit immunogenicity [6, 82].

Future developments of stimuli-responsive nanoparticles could also improve therapeutic localization, enabling drug delivery with spatial and temporal control in response to pathological conditions such as pH variations, oxidative stress, enzymes, or externally applied physical stimuli. Nonetheless, further evolution should address reliability and predictability in the context of a clinically relevant condition [19].

The integration of computational modeling, artificial intelligence, and machine learning into nanoparticle design is a promising way to accelerate translation. The application of data methods can optimize physicochemical parameters, predict biodistribution, toxicity, and therapeutic performance, and eliminate the need for trial-and-error experimentation [57, 74, 91]. Individualized nanomedicine approaches tailored to a patient's unique disease characteristics could even enhance effectiveness, but they will require powerful biomarkers, scalable production, and adaptive regulatory systems [27, 65, 79].

However, successful translation of these emerging strategies will depend on demonstrating reproducibility, scalable manufacturing, and clear clinical benefit in human-relevant models.

CONCLUSION

The relatively low clinical efficacy of nanoparticle-based therapies for brain diseases is not a failure of nanotechnology itself, but a conflict between the priorities in experimental design and the actual biology of disease and complex regulatory restrictions. The heterogeneity of the BBB and systemic

fate, as well as the design heterogeneity of nanomedicine, can be directed to counteract the problem of brain nanomedicine going beyond a successful proof-of-concept.

Another avenue for nanoparticle application in brain disease lies in improving drug delivery and imaging; however, translation remains constrained by biological variability, immune clearance, safety concerns, and regulatory challenges [79, 85, 94]. Experience increasingly shows that BBB penetration alone does not predict therapeutic success, particularly in chronic neurological disorders. Platforms that balance biological performance with manufacturability, regulatory clarity, and long-term safety are more likely to advance to clinical trials than highly complex, multifunctional systems [57, 79, 91].

Clinical experience indicates that successful brain nanomedicine requires not only BBB penetration but also effective interstitial distribution and cellular-level drug delivery within the human brain.

AI Tool Declaration: In accordance with the journal's editorial policy, the authors disclose the use of artificial intelligence tools in the preparation of this manuscript. ChatGPT (Model GPT-5.2) was used solely for language refinement and grammatical polishing of the final draft; the scientific content and structure remain the original work of the authors. Additionally, the Graphical Abstract was generated using Google Gemini (Model Gemini 2.5 Flash Image) based on the authors' original conceptual sketches and specific scientific constraints. The authors have meticulously verified the generated imagery to ensure it accurately represents the biological mechanisms described and accept full responsibility for its content.

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