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Review Article

Functional nanomaterial strategies for targeted CNS drug delivery

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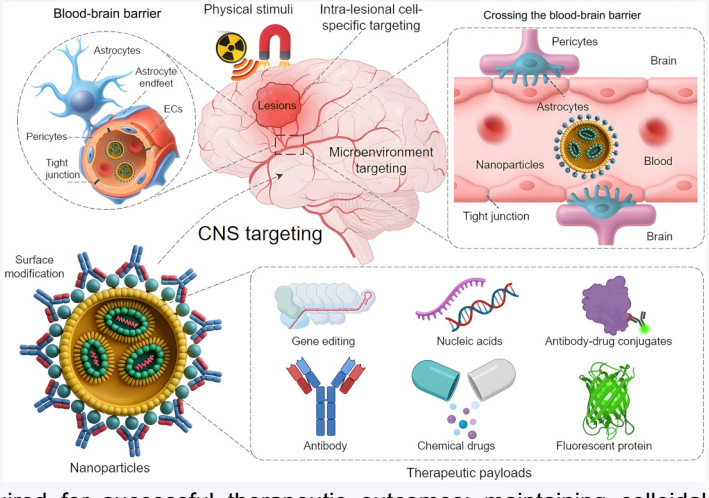
ABSTRACT: Effective therapeutic intervention for central nervous system (CNS) diseases, including brain tumors and neurodegenerative disorders, is significantly challenged by the formidable blood-brain barrier (BBB). This biological barrier severely restricts the passage of most drug candidates, resulting in inefficient delivery to pathological sites and substantially contributing to high clinical trial failure rates for CNS therapies. Engineered nanoparticles have emerged as promising functional material systems capable of navigating these delivery obstacles, offering advantages like encapsulating diverse agents, controlled release, and targeted delivery. This review comprehensively analyzes innovative nanoparticle strategies specifically designed to overcome the BBB and achieve precise CNS delivery via systemic administration. We highlight the critical multi-step biological cascade required for successful therapeutic outcomes: maintaining colloidal stability in circulation, efficiently penetrating the BBB, achieving specific accumulation at the disease site, and effectively engaging target cells. Despite significant advancements, clinical translation of these nanoparticle systems remains limited. A thorough understanding of this multi-step process is paramount to accelerating the clinical application of brain-targeted nanomedicines.



KEYWORDS: blood-brain barrier (BBB), nanoparticles (NPs), central nervous system (CNS) drug delivery, targeted delivery, systemic administration

1 Introduction

Central nervous system (CNS) diseases, encompassing devastating conditions such as brain tumors and neurodegenerative disorders, continue to pose a formidable challenge to human health [1, 2]. Despite considerable advancements in understanding CNS pathology, effective therapeutic interventions are often significantly limited by the highly selective blood-brain barrier (BBB). This leads to suboptimal drug concentrations at disease sites [3] and contributes to substantially higher clinical trial failure rates for neurodegenerative therapies compared to non-CNS conditions [4, 5].

Addressing these critical delivery obstacles necessitates innovative strategies grounded in advanced functional materials.

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Engineered nanoparticles (NPs) have emerged as highly promising functional material systems, undergoing rapid development over the past decade for diverse therapeutic and diagnostic applications within the CNS [6]. These versatile nanocarriers offer inherent advantages driven by their designed properties, including the capacity to encapsulate a wide range of therapeutic agents, from small molecules to biotherapeutics, provide precise controlled-release kinetics, and facilitate active or passive targeted delivery. Consequently, they represent a major focus of research aimed at enabling efficient BBB penetration and achieving specific drug distribution to targeted brain regions or cell types [7].

While nanocarriers (NCs) can be administered via various routes, including intranasal [8], intrathecal [9], and intracerebroventricular delivery [10], systemic administration remains the most clinically relevant and widely employed approach, particularly given the brain's substantial blood supply (nearly 20% of total cardiac output) [11]. Achieving optimal therapeutic efficacy and minimizing off-target effects for systemically administered brain-targeted NC systems requires successful navigation of a complex, multi-step biological cascade. This sequence involves: 1) maintaining colloidal stability within the bloodstream to prevent aggregation and premature clearance, 2) efficiently penetrating the BBB, 3) achieving specific accumulation at the pathological site within the brain parenchyma, and 4) precisely engaging target cells for effective drug delivery and release at the intended destination.

Despite considerable efforts in engineering diverse NP systems for enhanced brain accumulation and targeting, translation to clinical trials remains significantly limited. Addressing this critical gap requires a deep understanding of the challenges and opportunities at each stage of the delivery process. This review therefore provides a comprehensive overview of innovative nanoparticle strategies specifically engineered to navigate these complex biological hurdles, with a particular emphasis on systemically administered approaches for targeted CNS drug delivery. Navigating this multi-step journey and developing corresponding materials engineering strategies are paramount to accelerating the clinical translation of brain-targeted nanomedicines (Fig. 1).

2 Navigating the systemic circulation: Pharmacokinetic challenges and nanomaterial design strategies

Upon entering the bloodstream, NCs must navigate the systemic circulation to reach brain. However, the fate of NCs in the circulation is tightly regulated by the interplay between their physicochemical properties and the complex biological system.

The initial step following entry into the bloodstream is the rapid interaction of NCs with plasma proteins and other biomolecules, resulting in the formation of a dynamic "protein corona" (PC) on their surface [12, 13]. The PC confers a new biological identity upon the NCs, significantly impacting their subsequent *in vivo* behavior [14]. The specific composition of the PC was found to be highly dependent on the intrinsic properties of the NCs, including size, shape, core composition, and surface chemistry, resulting in considerable heterogeneity in the coronas formed on different types of NCs [15, 16]. Crucially, the PC may become enriched with opsonins, proteins that tag the NCs for recognition and subsequent phagocytosis by the mononuclear phagocyte system (MPS) [17]. The MPS, primarily comprising Kupffer cells in the liver along with tissue-resident macrophages in the spleen, lungs, and bone marrow,

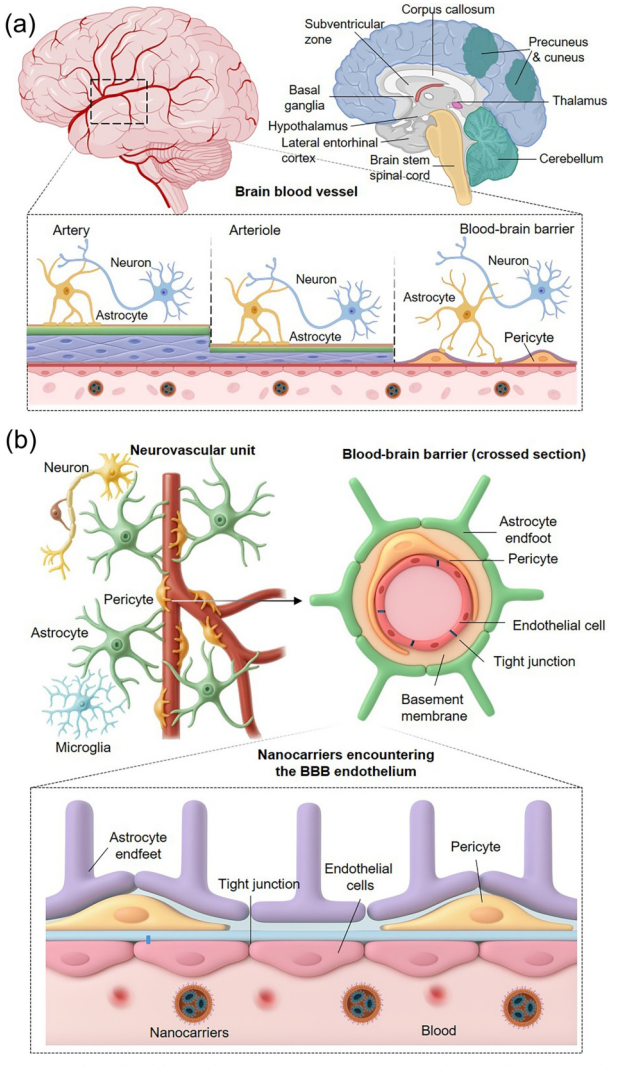

Figure 1 The blood-brain barrier (BBB): structure and its role in impeding nanoparticle delivery. (a) Anatomical context of the central nervous system (CNS), showing the human brain and its major vascular supply within the cerebrum. (b) Cellular architecture of the neurovascular unit (NVU) and blood-brain barrier, illustrating the impediment to nanocarrier delivery. Left: composition of the NVU surrounding a brain microvessel, including neurons, astrocytes, pericytes, and microglia. Middle: magnified view of the BBB detailing key components: endothelial cells connected by specialized tight junctions (severely restricting paracellular transport), the basement membrane, pericytes embedded within the basement membrane, and astrocytic end-feet ensheathing the vessel. Bottom: nanocarriers circulating within the bloodstream encountering the BBB endothelium, highlighting the challenge in traversing this highly selective barrier to reach the brain parenchyma.

possesses potent phagocytic capabilities and efficiently clears exogenous substances from circulation [18]. Consequently, the MPS often rapidly clears a significant fraction of intravenously injected NCs [19, 20], with hepatic capture being particularly prominent, sometimes accounting for up to 90% of the administered dose [21–23].

In addition to MPS-mediated clearance, renal excretion represents another critical factor governing the circulation longevity of NCs. The glomerular filtration barrier (GFB) exhibits size-selective permeability, permitting the free passage of small molecules and water while restricting the filtration of larger entities like macromolecules and proteins. Typically, NCs with

hydrodynamic diameters smaller than approximately 5–8 nm were shown to readily pass through the GFB, leading to their rapid renal clearance [24, 25], whereas larger NCs are generally retained in circulation.

To overcome these clearance mechanisms and prolong the circulation time of NCs, various optimization strategies have been developed. These strategies primarily focus on two aspects: modulation of physicochemical property and surface modifications. An ideal NC size is generally considered to be within the 10–200 nm range [26] to balance MPS-mediated clearance and renal excretion. Regarding shape, studies indicated that non-spherical NCs (e.g., ellipsoidal or worm-like morphologies) experienced reduced macrophage phagocytosis and exhibited an increased tendency for margination and adhesion to vessel walls compared to their spherical counterparts [27–29]. Maintaining a surface charge that is near-neutral or slightly negative was reported to reduce non-specific adsorption of serum proteins, thereby diminishing the likelihood of recognition and uptake by the MPS [30, 31]. Recently, building upon a deeper mechanistic understanding of specific protein corona-receptor interactions, a novel "decoy nanoparticle" strategy has emerged. The core of this strategy lies in the pre-design and construction of decoy nanoparticles surface-functionalized with specific receptor-associated corona ligands (RACLs). The primary role of these decoy particles *in vivo* is to preferentially bind to corresponding receptors on phagocytic cells, such as liver macrophages, thereby achieving pre-saturation of these receptors. Through this "pre-treatment" or "priming" of the liver, subsequently administered therapeutic nanoparticles are less susceptible to hepatic capture, consequently allowing more nanoparticles to target extrahepatic tissues [32].

Among surface modification techniques, functionalization via covalent or non-covalent conjugation of specific molecules is common. The most widely adopted strategy has been PEGylation, which involves modifying the NC surface with polyethylene glycol (PEG). This process creates a hydrophilic hydration layer that sterically hinders protein adsorption and significantly prolongs circulation half-life [33, 34]. More sophisticated, advanced strategies include biomimetic camouflage. Examples involved decorating NCs with CD47 mimetic peptides, known as "self-markers" or "don't eat me" signals [35], or cloaking NCs entirely with cell membranes derived from sources such as red blood cells, platelets, or macrophages [36–40]. These biomimetic approaches aim to enable the NCs to mimic endogenous cells, thereby potentially evading recognition and clearance by the host immune system (Fig. 2).

3 Overcoming the blood-brain barrier: Mechanisms and engineered nanomaterial strategies

The BBB constitutes a formidable physiological impediment to effective drug delivery to the brain parenchyma. Structurally, the BBB comprises brain endothelial cells (BECs), which are interconnected by intricate tight junctions, and is further supported by a basement membrane, pericytes, and closely associated astrocytic end-feet [41]. The non-fenestrated nature of these endothelial cells, coupled with their luminal tight junctions, establishes a robust physical barrier that severely restricts the paracellular transport of most macromolecules and hydrophilic substances. While small lipophilic molecules (typically < 400 Da) can traverse the BBB via passive diffusion, larger entities such as NCs must predominantly rely on active transcytosis mechanisms [42]. BECs have been shown to possess various pathways for transcytosis, including carrier-mediated transport (CMT), adsorptive-mediated transcytosis (AMT), and receptor-mediated transcytosis (RMT), each exhibiting specificity for different types of macromolecules. However, even when NCs successfully reach the

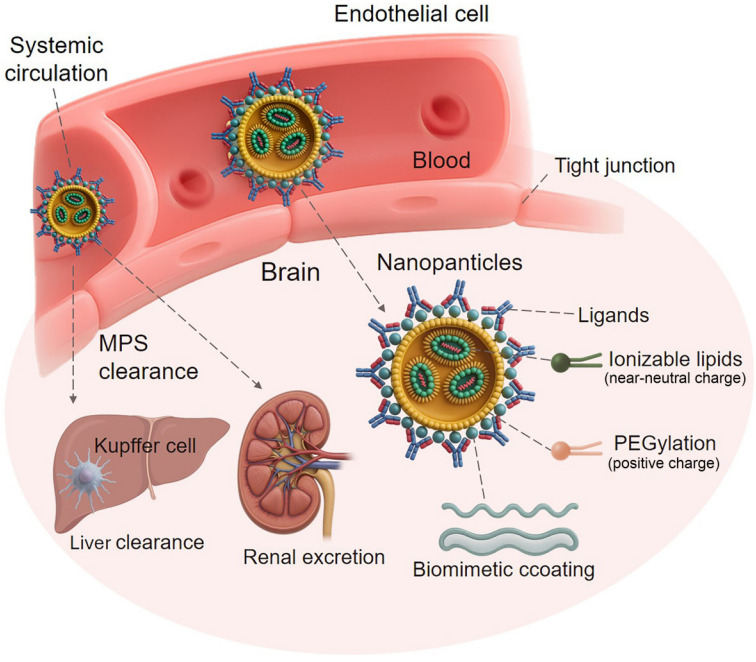

Figure 2 Strategies for engineering nanoparticles to overcome biological barriers for brain delivery. This schematic depicts the fate of a nanoparticle in systemic circulation and the design principles for enhancing its delivery to the brain. In the bloodstream, the particle faces clearance via the mononuclear phagocyte system (MPS) (e.g., Kupffer cells in the liver) and renal excretion. To improve its pharmacokinetic profile and facilitate transport across the blood-brain barrier's endothelial cells and tight junctions, the nanoparticle surface is modified with targeting ligands, shielding polymers (PEGylation), biomimetic coatings, and ionizable lipids that confer a near-neutral charge. These modifications aim to reduce clearance and enhance specific uptake in the brain.

BEC surface, the overall rate of transcytosis often remains suboptimal, and considerable heterogeneity in uptake has been observed across the brain vasculature. Furthermore, the efficiency of delivery can be significantly curtailed by the action of efflux transporters embedded within the BBB, such as members of the ATP-binding cassette (ABC) transporter family, which actively pump substrates, potentially including NCs or their cargo, back into the bloodstream [43, 44].

Although the intact BBB presents a significant hurdle, its structural and functional integrity is frequently compromised in various CNS disorders. Pathological conditions can induce endothelial cell damage, reduce the integrity of tight junctions, cause alterations in the basement membrane, and lead to the detachment of pericytes and astrocytic end-feet; collectively, these changes often result in increased BBB permeability [45–47]. This increased permeability might create opportunities for enhanced NC penetration into the brain parenchyma. However, the situation is complex, as the pathological state can also induce significant changes in the expression levels of specific transporters and receptors on the BBB, potentially diminishing the effectiveness of active targeting strategies that rely on these mechanisms [34, 48, 49]. Therefore, developing successful strategies for NC transcytosis requires a comprehensive understanding of both the normal BBB and the specific pathological changes caused by the target disease. This understanding is therefore critical for the rational design of effective brain delivery systems.

3.1 Passive targeting

Passive brain targeting strategies leverage the tendency of NCs to preferentially accumulate in brain tissue, a process primarily driven by their intrinsic physicochemical properties interacting with the altered microenvironment often found in pathological brain states, which can include increased vascular permeability and reduced lymphatic drainage (often termed the enhanced permeability and retention, or EPR-like, effect in the brain) [50]. Despite this potential advantage, it is crucial to recognize that passive targeting generally results in limited translocation of NCs across the intact or even compromised BBB. Even under disease conditions where permeability may be increased, the BBB typically retains significant barrier function, representing a substantial obstacle for NC delivery. Therefore, achieving meaningful improvements in brain accumulation via passive mechanisms necessitates careful design and optimization of the NCs' fundamental physicochemical characteristics.

3.1.1 Particle size

Particle size is a critical determinant of NC fate *in vivo* and their ability to cross the BBB. Generally, NPs smaller than 100 nm have been considered more advantageous for BBB transit [51]. Indeed, some investigations indicated that even smaller sizes, such as those below 50 nm, could facilitate brain entry via mechanisms like endocytosis and transcytosis. For instance, one study reported that drug-loaded polymeric nanoparticles with a 20 nm diameter demonstrated greater BBB penetration and subsequent drug accumulation in the brain compared to their 50 and 100 nm counterparts [51]. However, the optimal size is not always the smallest. A separate study involving mesoporous silica nanoparticles (MSNs) found that 50 nm MSNs exhibited superior BBB penetration relative to both 20 and 100 nm variants [52].

Furthermore, the influence of pathological conditions must be considered. The EPR effect, characterized by leaky vasculature and impaired drainage, might favor the passive accumulation of slightly larger nanoparticles (e.g., in the 100–200 nm range) within diseased brain regions. Following traumatic brain injury, for example, it was observed that smaller nanoparticles showed a greater propensity to cross the BBB and distribute more broadly throughout the brain parenchyma, whereas larger nanoparticles tended to accumulate preferentially in areas exhibiting more pronounced BBB disruption [53]. This suggests that optimal size may depend on both the NC type and the specific pathological context.

3.1.2 Lipophilicity and hydrophilicity

The balance between hydrophilicity and lipophilicity profoundly impacts NC behavior. While hydrophilic NCs generally exhibit improved stability in the bloodstream and reduced clearance by the MPS, their weak interaction with the lipophilic bilayer of BEC membranes often resulted in limited BBB penetration [54]. Conversely, lipophilic NCs can interact more readily with the endothelial cell membrane, potentially enhancing BBB transit. However, excessive lipophilicity was found to sometimes lead to NC entrapment within the cell membrane itself, paradoxically diminishing overall penetration efficiency and potentially increasing the risk of cytotoxicity. Consequently, amphiphilic NCs, which strategically incorporate both hydrophilic and lipophilic moieties, represent a balanced approach. This design aims to maintain bloodstream stability while simultaneously promoting productive interactions with the endothelial cell membrane, thereby potentially enhancing transcytosis efficiency [55, 56].

3.1.3 Surface charge

Historically, cationic NCs were often considered advantageous for promoting endocytosis or transcytosis due to their electrostatic attraction to the generally anionic cell membranes [57–59]. However, a significant drawback reported for cationic NCs was their potential to induce cytotoxicity and disrupt BBB integrity [60]. Conversely, anionic NCs were thought to potentially encounter difficulty approaching the cell membrane due to electrostatic repulsion [61].

This apparent dichotomy led to the development of dynamic charge modulation strategies as a promising alternative. A typical design involved engineering NCs to maintain a neutral or slightly negative charge during systemic circulation, thereby minimizing non-specific protein adsorption and MPS uptake to extend circulation time. Upon approaching the BBB microenvironment, the charge was designed to shift towards a slightly positive state, enhancing interactions with endothelial cells and promoting transcytosis [62, 63].

However, more recent investigations have suggested a more nuanced role for surface charge. Studies involving MSNs within specific size ranges indicated that even NPs bearing a negative charge could effectively cross the BBB. This phenomenon was potentially attributed to the adsorption of specific plasma proteins onto the mesoporous structure, effectively masking the intrinsic charge and modifying the NP's biological identity. Further research suggested that particle size and charge might act synergistically to influence BBB penetration; for certain sizes of MSNs, a negative charge did not significantly impede, and in some contexts might have even enhanced, transport across the BBB [64].

Therefore, the influence of surface charge on nanocarrier BBB crossing is clearly not governed by a simple linear relationship

but is rather a complex, multifactorial process. Optimal surface charge design requires careful consideration integrated with other factors, such as the specific NC material, core/cargo properties and particle size.

3.1.4 Shape

Beyond size and surface chemistry, the geometric shape of NCs, particularly their surface topology, has emerged as another critical factor influencing BBB crossing efficiency. For example, virus-like silica NPs engineered to possess rough, "spiky" surfaces demonstrated markedly enhanced BBB penetration compared to their smooth-surfaced counterparts of similar overall size. This improved transit was attributed to the increased physical interaction points provided by the spiky structures engaging with the endothelial cell membrane, which was proposed to promote the transient opening of tight junctions [65]. This highlights that nanoscale morphology itself can be engineered to modulate interactions at the BBB interface (Table 1 and Fig. 3).

3.2 Active targeting

Active targeting strategies utilize specific biological recognition mechanisms or engineered functionalities to enhance the transport of therapeutics across the BBB. This approach relies on high-specificity interactions, wherein NCs are designed to engage with endogenous transporters, receptors, or other energy-dependent processes expressed on the BBB endothelium, thereby facilitating their passage into the brain parenchyma.

3.2.1 Receptor-mediated transcytosis (RMT)

Among active targeting approaches, RMT represents the most extensively investigated strategy. RMT operates through a specific sequence of events initiated by the binding of a ligand to its cognate receptor on the BEC surface. This binding typically triggered the formation of a clathrin-coated pit, which subsequently invaginated to form an endocytic vesicle. Critically, during intracellular trafficking, this vesicle must evade lysosomal degradation and ultimately traffic across the endothelial cell to release its cargo into the brain parenchyma via exocytosis on the abluminal side. This pathway offers high selectivity and efficiency for transporting specific macromolecules across the BBB.

For optimal BBB penetration via RMT, an ideal target receptor should exhibit high expression density on BECs, particularly within the extensive microvascular capillary network, while displaying minimal expression in peripheral tissues to mitigate off-target effects and associated safety concerns. However, identifying a protein that perfectly meets these criteria has proven challenging [67]. Consequently, research over the past decades has predominantly focused on targeting receptors known to be expressed on BBB cells, even if ubiquitously, such as the transferrin receptor (TfR), the low-density lipoprotein receptor (LDLR) family and the integrins.

(1) Transferrin receptor (TfR)

The transferrin receptor (TfR) remains a prominent target for RMT-based brain delivery. Research targeting TfR has progressed through several stages. Early efforts often utilized murine monoclonal antibodies, such as OX26 [68] and 8D3 [69]. To address potential immunogenicity and the steric hindrance associated with large antibodies, subsequent work focused on developing smaller, engineered antibody fragments [70–72]. Further refinements included the design of bispecific antibodies, engineered not only to enhance BBB penetration via TfR binding but also to engage therapeutic targets within the brain parenchyma [73]. Beyond antibody-based strategies, TfR-binding peptides and natural ligand analogs, such as human heavy-chain ferritin (HFn) [74], have also demonstrated promising results, showing efficient brain targeting and, notably, low immunogenicity.

Extensive research has also focused on optimizing NC design parameters to improve the efficiency of TfR-mediated delivery. For example, studies showed that precise control over the density of TfR-targeting antibodies displayed on the NP surface could significantly enhance BBB penetration [75]. Simultaneously, achieving a balance between antibody affinity and valency was found to be crucial: high-affinity, bivalent antibodies often led to the TfR-antibody complex being sorted towards lysosomal degradation, whereas monovalent formats or antibodies with low-to-moderate affinity appeared to better facilitate entry into the productive transcytotic pathway, thereby improving overall transport efficiency [71, 76, 77].

To overcome the common challenge of lysosomal entrapment associated with TfR targeting, researchers have explored several innovative strategies. One approach employed acid-sensitive linkers to dynamically conjugate transferrin to an NP core. This design allowed the nanosystem to trigger ligand dissociation within the acidic environment (pH ≈ 5.5) of endosomes inside BECs, enabling the NPs to potentially escape lysosomal sorting signals and preferentially enter the transcytotic route [78]. More recently,

Table 1 Key nanoparticle properties and modifications influencing CNS delivery

Property/ modification	Advantages	Limitations & considerations	Ref.
Particle size	Small (< 50 nm): enhanced BBB transcytosis. Large (100–200 nm): benefits from EPR-like effect in diseased tissue.	Too small (< 8 nm): rapid renal clearance. Optimal size is context-dependent (material, disease state).	[51–53]
Surface charge	Cationic (+): promotes electrostatic cell interaction & uptake. Dynamic/switchable: balances circulation stability with targeted uptake at the BBB.	Cationic (+): high cytotoxicity; non-specific protein binding; rapid clearance. Anionic (−): potential electrostatic repulsion from cell membranes.	[57–64]
Shape/ morphology	Non-spherical (e.g., spiky, rod): increased physical interaction with endothelium; potential modulation of tight junctions.	Effects are material-dependent and less understood. Manufacturing and scalability challenges for complex shapes.	[65]
Surface modification	Stealth (e.g., PEG): prolonged circulation; reduced MPS uptake. Biomimetic (cell membrane): immune evasion; confers natural cell-homing functions. Active targeting (ligands): enables receptor-mediated transcytosis for high specificity.	Stealth coatings: can cause steric hindrance for ligands ("PEG dilemma"). Protein corona: can mask targeting ligands, reducing efficacy. Complexity: requires optimization (ligand density, affinity); risk of off-target effects.	[66]

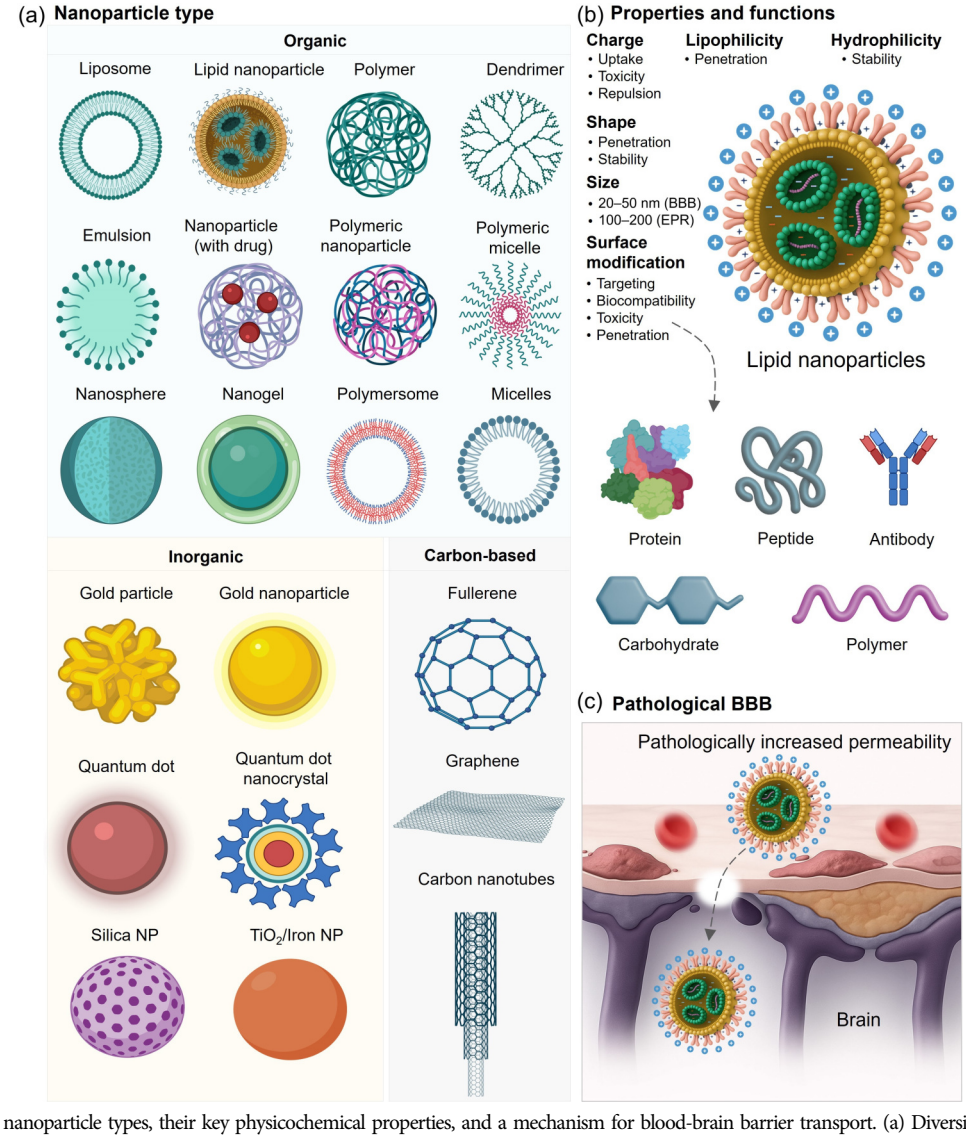

Figure 3 Diversity of nanoparticle types, their key physicochemical properties, and a mechanism for blood-brain barrier transport. (a) Diversity of nanoparticle types. This panel displays a classification of various nanocarriers based on their core material. The categories include: organic (e.g., liposomes, lipid nanoparticles, polymeric micelles, polymersomes), inorganic (e.g., gold particles, quantum dots, silica NPs, TiO_2/Iron NPs), and carbon-based (e.g., fullerenes, graphene, carbon nanotubes). (b) Key properties and functional modifications of nanoparticles. Using a lipid nanoparticle as a central example, this panel outlines the tunable physicochemical properties that dictate a nanoparticle's behavior, including charge, shape, size, lipophilicity, and hydrophilicity. Furthermore, it illustrates molecules commonly used for surface modification to impart specific functions, such as targeting or enhanced biocompatibility. These modifiers include proteins, peptides, antibodies, carbohydrates, and polymers. (c) Nanoparticle transport across a pathological BBB. This panel illustrates a key mechanism of nanoparticle entry into the brain, where certain pathological conditions lead to increased permeability of the BBB. This compromised barrier integrity allows nanoparticles to pass through the otherwise restrictive endothelial layer and accumulate in the brain tissue.

researchers engineered NCs derived from HFn by truncating its C-terminus. This modification was designed to create a weak-acid-responsive disassembly mechanism, whereby the modified ferritin rapidly disassembled within the acidic milieu of lysosomes, exposing internal positive charges intended to facilitate lysosomal escape [79].

(2) Low-density lipoprotein receptor (LDLR) family

The low-density lipoprotein receptor (LDLR) family comprises a group of transmembrane glycoproteins highly expressed on BECs. This family includes LDLR itself, low-density lipoprotein receptor-related protein 1 (LRP-1), LRP1B, megalin/LRP2, very low-density lipoprotein receptor (VLDLR), apolipoprotein E receptor 2 (ApoER2/LRP8), sortilin-related receptor (SorLA/LR11), LRP5, and LRP6. These receptors were known to mediate the endocytosis of a diverse array of ligands, including various apolipoproteins, p97 (melanotransferrin), and vasoactive intestinal peptide.

Among the ligands recognized by the LDLR family, Angiopep-2 (ANG2) and apolipoprotein E (ApoE) emerged as prominent LRP ligands extensively investigated for constructing brain-targeting NCs. Studies demonstrated that conjugating these ligands to NCs mediated specific binding to LRP, facilitating BBB penetration via the RMT pathway [80–86]. Furthermore, this strategy offered the potential for dual targeting: initial transcytosis across the BBB via LRP engagement, followed by enhanced local drug accumulation through subsequent recognition of LRP or related receptors expressed at pathological sites, such as glioma cells or amyloid-β plaques [87].

Technological advancements targeting LDLR ligands have primarily focused on two areas. The first involved ligand engineering and optimization. For example, For example, by synthesizing retro-inverso isomers of ANG2 (e.g., DANG [80] or D-Angiopep [88]), where the L-amino acid sequence was inverted and substituted with D-amino acids, researchers created peptides that retained high-affinity binding to LRP-1 but exhibited significantly improved resistance to enzymatic degradation, thereby prolonging their *in vivo* half-life. A second major frontier has been extending the cargo capacity beyond small molecules to challenging biotherapeutics. For instance, ANG2-modified NPs have successfully delivered galactocerebrosidase (GALC) and significantly restored enzyme activity in the brains of Krabbe disease model mice [89]. Moreover, inspired by the budding mechanism of neuronal membranes, researchers developed biomimetic carriers exploiting lipid raft self-assembly, functionalized with ApoE3 and αRAP peptides. These carriers achieved efficient delivery of brain-derived neurotrophic factor (BDNF) and demonstrated potential for symptom amelioration in Alzheimer's disease (AD) models [90].

(3) Integrins

Integrins constitute another crucial class of transmembrane receptor glycoproteins widely expressed on BECs. Notably, reports indicated that their expression levels and subtype composition could change significantly in the context of brain pathologies such as tumors and stroke [91]. Leveraging this differential expression, researchers have developed integrin-ligand-modified NCs for active targeting across the BBB.

The arginine-glycine-aspartic acid (RGD) tripeptide sequence and its analogs have been widely utilized due to their established ability to specifically recognize multiple integrin subtypes. Studies showed that conjugating RGD, particularly in its cyclic form (cRGD), to NC systems could enhance BBB penetration efficiency. In one innovative example, cRGD-functionalized liposomes were demonstrated to "hitchhike" on circulating leukocytes; these leukocytes, expressing high levels of αvβ3 integrin, then transmigrated across the compromised BBB in ischemic stroke models, carrying the liposomes with them [92]. Furthermore, exploiting the genetic malleability of ferritin, researchers developed an integrin α2β1-targeting H-ferritin-based NP platform. These NCs were engineered not only to display a specific integrin-binding peptide on the HFn surface for tumor targeting but also to retain the inherent TfR1-mediated BBB crossing capability of ferritin, thereby establishing a dual-targeting mechanism [74].

3.2.2 *Carrier-mediated transport (CMT)*

CMT represents another key strategy for facilitating drug or NC delivery across the BBB by utilizing specific endogenous carrier proteins embedded within the endothelial cell membranes. This process typically involves several stages: First, carrier proteins expressed on the BBB, such as the glucose transporter GLUT1 or the amino acid transporter LAT1, recognize and bind to their specific substrates or appropriately designed analogs. Subsequently, the carrier protein undergoes a conformational change, facilitating the translocation of the bound substrate across the BBB. Finally, upon reaching the brain side, the carrier protein releases the substrate and reverts to its initial conformation, ready for another transport cycle. Several carrier systems have been commonly exploited for CMT at the BBB, with GLUT1 and LAT1 being prominent examples.

(1) Glucose transporter 1 (GLUT1)

Targeting the glucose transporter GLUT1 leverages its primary function of supplying glucose to the brain. Delivery strategies based on GLUT1 typically involved designing therapeutics or NCs that mimic glucose [93] or display other GLUT1 ligands, such as mannose [94], enabling binding to the transporter and subsequent transport into the brain. This approach capitalized on the high expression levels of GLUT1 on BBB endothelial cells and its natural transport capacity. However, significant limitations were associated with this strategy. First, the transport efficiency via GLUT1 is inherently constrained by substrate competition (particularly from endogenous glucose) and saturation kinetics. For instance, studies indicated that physiological fluctuations in blood glucose levels could significantly impact the delivery efficiency of nanoparticles modified with glucose analogs [95]. Second, reliance on unidirectional transport via GLUT1 often made it difficult to achieve precise targeted distribution of drugs within the brain parenchyma, and the heterogeneity frequently observed in pathological microenvironments could further complicate predictable delivery.

Despite these challenges, innovative delivery strategies developed in recent years have shown progress in addressing the traditional bottlenecks of GLUT1-mediated brain targeting. One research group developed a novel glycosylated, triple-force-stabilized siRNA nanodrug (Gal-NP@siRNA) designed to target β-secretase 1 (BACE1) for potential Alzheimer's disease (AD) treatment. This nanodrug utilized surface glycosylation (Gal) to engage GLUT1 on BBB endothelial cells, thereby promoting siRNA penetration across the barrier. Significantly, this approach cleverly leveraged the known upregulation of GLUT1 activity under hypoglycemic conditions to achieve enhanced delivery via transporter recycling. This was reportedly accomplished by first inducing transient hypoglycemia (to increase GLUT1 surface expression on the luminal side), followed by glucose replenishment. As GLUT1 subsequently recycled towards the abluminal membrane, the glucose-modified nanocarriers were proposed to be co-transported across the BBB with markedly improved efficiency [96]. Another representative study proposed an oral delivery strategy employing NPs externally modified with mannose. These NPs were specifically designed for use in conjunction with a glycemic control regimen. This controlled glucose level was reported as key, as it allowed the mannose-functionalized nanoparticles to effectively 'hitchhike' the GLUT1 transport cycle across the BBB [94].

(2) L-type amino acids transporter 1 (LAT1)

LAT1, an amino acid transporter, primarily transports large neutral amino acids like tyrosine, phenylalanine, and tryptophan across the BBB. Carrier-mediated transport (CMT) strategies targeting LAT1 typically involve LAT1 substrates: Drugs are either designed as LAT1 substrate analogs or conjugated to LAT1 substrates. Examples reported in the literature included liposomes modified with glutamic acid intended for glioma treatment [97], and NPs conjugated with tyrosine derivatives [98] or L-phenylalanine [99]. However, a major challenge frequently encountered with this approach was the significant competition from endogenous amino acids. These endogenous substrates are present at much higher physiological concentrations in the blood and were shown to potentially reduce the BBB penetration efficiency of NCs designed to engage LAT1 [100]. Consequently, future research in this area is anticipated to focus on strategies such as optimizing the conformation and presentation of amino acid conjugates on NCs to enhance their binding affinity and selectivity for LAT1 relative to

endogenous competitors.

3.2.3 *Protein corona (PC)-mediated active targeting*

The formation of a PC upon NC entry into the bloodstream has traditionally been viewed as a significant obstacle, particularly for "active targeting" strategies. This perception stemmed from the understanding that engineered surface modifications on NCs, intended for targeting, could inadvertently promote the adsorption of plasma proteins through charge interactions or other intermolecular forces, subsequently forming a complex and dynamic PC [66]. It was thought that this adsorbed protein layer could sterically hinder the targeting ligands, thereby reducing the tissue-homing efficiency and specificity of the NCs and ultimately impeding their ability to cross the BBB [101, 102].

However, the understanding of the PC's role has undergone a fundamental shift in recent years. Research is increasingly focused not merely on inhibiting protein adsorption but on strategically modulating or even harnessing functional protein coronas for delivery purposes. The PC is no longer viewed solely as detrimental but is recognized as possessing the potential to act as a "biological bridge," facilitating NC transport across the BBB. The work of Zhan's group exemplifies this evolving paradigm. Their early studies investigated CDX, a long, stable, cationic peptide. Although CDX demonstrated brain-targeting capabilities, it also led to increased IgM adsorption, which resulted in reduced immunocompatibility [103]. Driven by this finding, they subsequently employed computer-aided design to create D8, a short peptide. When conjugated to NCs, D8 reportedly minimized unfavorable protein adsorption, thereby improving both brain targeting efficiency and immunocompatibility [104]. Building on this line of research, and inspired by the known interaction between Aβ1-42 and apolipoprotein lipid-binding domains, they developed SP-sLip. This liposome formulation was designed to selectively adsorb specific beneficial apolipoproteins (A1, E, and J) from plasma. This strategy, which aligned with the concept of "endogenous targeting" described by a recent review where the NP surface is engineered to interact with specific blood proteins acting as targeting ligands [Hadjidemetriou, M., Mahmoudi, M. & Kostarelos, K.] *In vivo* biomolecule corona and the transformation of a foe into an ally for nanomedicine [105], aimed to create a tailored, functional PC on the NC surface that could actively mediate BBB penetration via engagement with corresponding endothelial receptors [104].

3.3 Cell-penetrating peptide (cpp)-mediated bbb penetration

CPPs are short amino acid sequences, typically ranging from 4 to 50 residues, that exhibit the notable ability to traverse cellular membranes and biological barriers. Based on their physicochemical characteristics, they can be broadly categorized as cationic, amphipathic, or hydrophobic peptides. Well-known examples include TAT (derived from the HIV transactivator of transcription) and penetratin. The precise mechanisms by which CPPs traverse the BBB remain complex and appear dependent on multiple factors, including the specific peptide sequence, concentration, the nature of the conjugated cargo, and the lipid composition of the target membrane [106]. Two principal pathways have been proposed: energy-independent direct membrane penetration [107] and various energy-dependent endocytic routes [108, 109].

The functionalization of NCs with CPPs has emerged as a promising strategy for enhancing brain-targeted drug and gene delivery. Research indicated that CPP modification could significantly augment the ability of NCs to penetrate the BBB [110, 111]. For instance, Wang et al. developed a liposome dually modified with transferrin and TAT, aiming for targeted delivery of a therapeutic gene to the mouse brain. Their results showed that this dual-functionalized liposome exhibited significantly higher gene expression levels in the brain compared to both unmodified liposomes and those modified solely with transferrin. This demonstrated that the CPP modification effectively promoted gene transport across the BBB and subsequent delivery into the brain parenchyma [111].

3.4 Cell-mediated BBB traversing

Coating NPs with biological cell membranes represents an innovative biomimetic strategy for facilitating BBB traversal. This approach aims to leverage the inherent properties, surface markers, and natural trafficking mechanisms of specific cell types to emulate or exploit cellular pathways across the BBB. A variety of cell membranes have been successfully employed to construct such biomimetic carriers, which have demonstrated enhanced BBB penetration capabilities in various studies.

For instance, NPs coated with red blood cell membranes, sometimes further modified with targeting ligands like Angiopep-2 or peptides, were shown to effectively penetrate the BBB [36, 40]. Similarly, macrophage membrane-coated delivery systems were proposed to function as "Trojan horses", utilizing the natural ability of macrophages to cross the BBB, particularly under inflammatory conditions, to breach the barrier [112]. Exploiting pathological mimicry, nanoparticles cloaked in membranes derived from brain-metastatic tumor cells were reported to mimic the BBB traversal behavior of the parent tumor cells, thereby effectively crossing the barrier [113]. Leveraging the barrier components themselves, nanoparticles coated with brain microvascular endothelial cell membranes demonstrated effective homotypic targeting to these endothelial cells, which facilitated efficient BBB crossing and subsequent accumulation in brain tumor models [114]. In a more complex example, nanorobots coated with NK cell membranes were engineered to possess surface-expressed biomimetic NK cell molecules. These molecules reportedly enabled interaction with cognate receptors on BBB endothelial cells and allowed the nanorobots to function as tight junction (TJ) modulators. This modulation was described as triggering an intracellular signaling cascade that caused transient TJ disruption and actin cytoskeleton reorganization. Essentially, they were proposed to create an intercellular "green channel", enabling efficient BBB crossing [115].

Collectively, these examples illustrate that cell membrane-coating technology, by emulating natural cellular transit mechanisms, exploiting specific cell-surface interactions, or even modulating barrier properties, offers a versatile and highly promising platform for achieving enhanced drug delivery to the brain (Fig. 4).

3.5 Physical stimuli for bbb penetration

Physical methods utilize external physical energy, such as ultrasound, light, and magnetic fields, to transiently modulate the BBB or enhance the transport of NCs across it into targeted brain regions.

3.5.1 *Focused ultrasound (FUS)*

The principal mechanism underlying FUS-mediated BBB

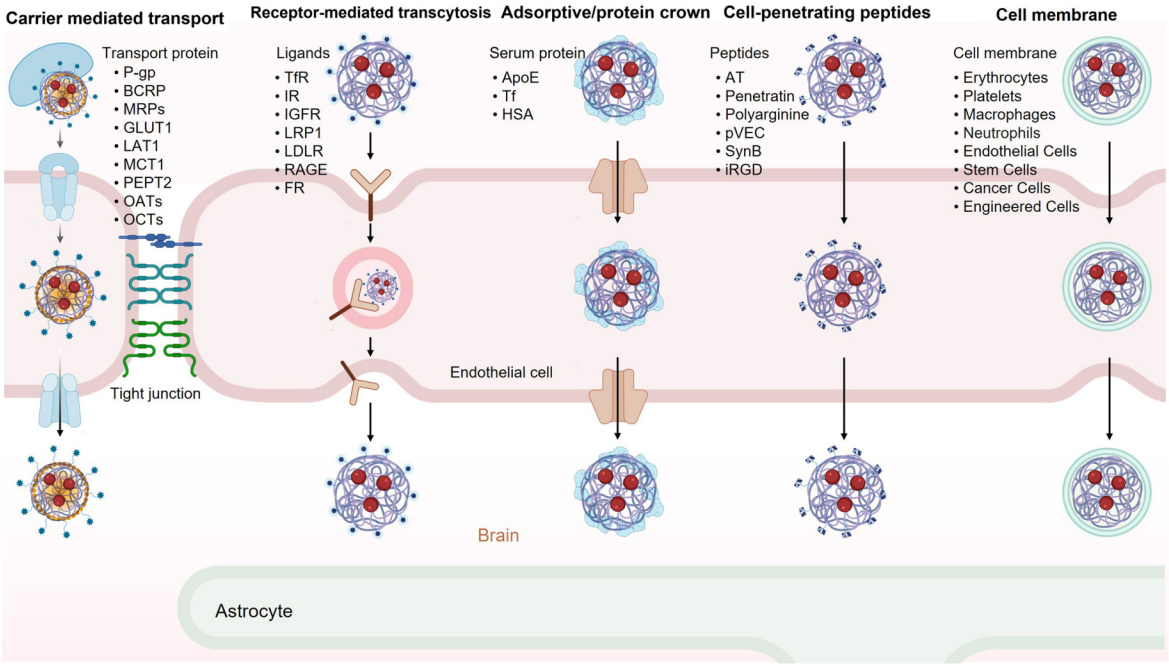

Figure 4 Engineered strategies for nanocarrier transport across BBB. Active strategies facilitating the passage of systemically administered NCs from the bloodstream into the brain parenchyma, overcoming the BBB endothelium: Carrier mediated transport: NCs or their cargo interact with specific influx transporters (e.g., P-gp, BCRP, MRPs, GLUT1, LAT1, MCT1, PEPT2, OATs, OCTs, OATPs) embedded within the endothelial cell membrane, utilizing carrier-mediated transport pathways. Efflux transporters, which pump substances out of the brain, are also depicted as a challenge. Receptor-mediated transcytosis: NCs surface-modified with specific ligands (e.g., TfR, IR, IGFR, LRP1, LDLR, RAGE, FR ligands) bind to corresponding receptors on the luminal surface of the BBB endothelium, triggering receptor-mediated endocytosis and transcytosis across the endothelial cell into the brain parenchyma. Adsorptive/protein crown mediated transport: NCs circulating in the blood adsorb serum proteins (e.g., ApoE, Tf, HSA) forming a protein corona, enabling interaction with specific receptors or transport systems on the BBB endothelium to facilitate NC uptake and transport into the brain. Cell-penetrating peptide-mediated transport: NCs associated with cell-penetrating peptides (CPPs) or other transport-enhancing peptides (e.g., AT, Penetratin, Polyarginine, pVEC, SynB, iRGD) interact with the endothelial cell membrane, promoting uptake and transport across the BBB. Cell membrane-coated nanoparticles: NCs encapsulated within vesicles derived from specific cell membranes (e.g., erythrocytes, platelets, macrophages, neutrophils, endothelial cells, stem cells, cancer cells, engineered cells), leveraging the inherent properties of these membranes to facilitate or enhance NC passage across the BBB.

disruption relies on the interplay between ultrasound waves and intravenously administered microbubbles (MBs). Within the targeted acoustic field, FUS induced high-frequency oscillations in the MBs, causing them to rapidly contract and expand. This mechanical activity generates localized shear stresses and microstreaming effects (microjets), which leads to the reversible opening of TJs between BBB endothelial cells, thereby significantly enhancing barrier permeability. Research demonstrated that this physical intervention could maintain a temporarily 'open' BBB state for approximately 1–4 h [116–118], creating a critical therapeutic window for NC delivery. For instance, studies reported that a single FUS treatment in conjunction with MBs could increase the brain delivery efficiency of macromolecules like antibodies or chemotherapeutic drugs by 3- to 5-fold compared to controls [119, 120].

To improve spatial precision and minimize potential off-target effects, FUS technology has been integrated with real-time magnetic resonance imaging (MRI) guidance. MRI-guided FUS allows for precise anatomical targeting of the BBB opening, dynamic monitoring of MB cavitation activity and drug distribution, and helps ensure that the acoustic energy is focused primarily on the intended area, thus minimizing the risk of damage to surrounding healthy brain tissue [121, 122]. This integrated approach offers a potentially efficient and safer strategy for achieving precise drug delivery to specific brain regions.

While FUS combined with MBs presents a promising avenue for delivering therapeutics across the BBB, concerns remain regarding potential bioeffects. Excessive acoustic energy was found capable of inducing sublethal cell damage or apoptosis [123]. The underlying mechanisms were thought to likely involve mechanical stress from ultrasonic cavitation, which could cause phosphatidylserine (PS) externalization on the cell membrane, triggering apoptotic signaling pathways. Furthermore, the inertial cavitation (rupture) of MBs was known to potentially release reactive oxygen species (ROS), exacerbating local oxidative stress and contributing to cell damage. To mitigate this potential cytotoxicity, researchers have focused on counteracting the oxidative stress associated with FUS-mediated BBB opening. One strategy involved encapsulating the antioxidant gastrodin (GAS) within a specialized NC system. This system was designed to facilitate efficient GAS release and delivery to the brain under FUS stimulation and MB cavitation. The delivered GAS then reportedly acted as a scavenger of the generated ROS, thereby affording protection to brain cells against oxidative damage during the BBB opening procedure [124].

3.5.2 *Light*

Light-based strategies primarily utilize photothermal or photodynamic effects to modulate BBB permeability. One core mechanism involves photothermal disruption. Specific nanomaterials, such as gold nanoparticles or black phosphorus nanosheets, are identified as possessing excellent photothermal conversion efficiencies. Upon illumination with light of a specific wavelength, typically in the near-infrared (NIR) spectrum for better tissue penetration, these materials could efficiently convert light energy into heat, generating localized hyperthermia. This mild,

controlled temperature elevation, often to 42–45 °C, has been proposed to trigger either the transient contraction or degradation of TJ proteins (e.g., ZO-1) in BECs, or to increase endothelial cell membrane fluidity. Consequently, BBB permeability can be temporarily enhanced, creating a "window of opportunity" for NC transcytosis [125–127].

Beyond the photothermal effect, photodynamic action offers another distinct mechanism for modulating the BBB. Photodynamic principles leverage the capacity of photosensitizers to generate cytotoxic ROS upon light activation. When a photosensitizer absorbs light energy of an appropriate wavelength, it can transfer this energy to adjacent oxygen molecules, resulting in the formation of ROS, such as singlet oxygen ($^1O_2$) and hydroxyl radicals (·OH). These highly reactive species have been shown to selectively damage cellular components, including TJ structures within BECs, thereby increasing BBB permeability [128, 129].

Building upon these individual mechanisms, researchers have explored synergistic approaches combining photothermal and photodynamic effects to potentially enhance BBB modulation efficiency. NCs for this purpose are typically designed to incorporate both photothermal agents and photosensitizers. Upon appropriate illumination, such systems could generate both heat and ROS simultaneously, providing a dual, and potentially more potent, modulatory effect on the BBB [130, 131]. For instance, one study described a dual-mode theranostic system based on upconversion nanoparticles (UCNPs), which could simultaneously activate co-loaded photosensitizers and photothermal agents under NIR irradiation, leading to enhanced BBB disruption through a proposed synergistic "thermal-oxidative" mechanism [130].

3.5.3 *Magnetic filed*

Magnetic fields offer another modality for influencing NCs delivery across the BBB. Under an alternating magnetic field (AMF), magnetic nanoparticles (MNPs) have been shown to absorb magnetic energy and convert it efficiently into heat via hysteresis loss or Neel/Brownian relaxation. This localized thermal effect, known as the magnetothermal effect or magnetic hyperthermia, when controlled to induce mild temperature elevations, typically 40–45 °C, could transiently increase BBB permeability, facilitating the entry of co-administered or MNP-based NCs into the brain [132, 133].

Distinct from the thermal mechanism employed by MNPs, magnetoelectric nanoparticles (MENs) leverage a non-thermal approach. MENs typically consist of a magnetostrictive core, which changes shape in a magnetic field, and a piezoelectric shell, which generates an electric potential when mechanically stressed. When exposed to an external magnetic field, often low-frequency AMF, MENs could generate transient, localized electric fields near the cell membrane. This localized electrical stimulation has been thought capable of inducing transient membrane permeability increases, potentially via mechanisms related to electroporation, thereby facilitating the passage of NCs or drugs across the BBB [134, 135].

3.5.4 *Low-dose radiation*

Low-dose radiation represents another physical method shown to enhance BBB penetration, primarily by modulating the physiological state of BECs rather than causing gross disruption. This approach leverages the reported ability of low-dose radiation to upregulate the expression of specific adhesion molecules or receptors on the endothelial cell surface, effectively creating enhanced "docking sites" for targeted drug delivery systems. A compelling example of this was demonstrated in the context of treating Sonic hedgehog (SHH)-subtype medulloblastoma. In this study, fucoidan-based NCs encapsulating the SHH pathway inhibitor vismodegib were designed to target P-selectin, which is expressed on activated endothelial cells. This interaction was shown to trigger caveolin-1-dependent transcytosis, actively transporting the nanocarriers into the brain tumor microenvironment. Crucially, pre-treatment with low-dose radiation was found to significantly potentiate this process by upregulating P-selectin expression, markedly improving the efficiency of NC penetrating the tumor-associated BBB. This radiation-enhanced targeted strategy resulted in striking therapeutic efficacy in preclinical animal models, underscoring the potential of using low-dose radiation to facilitate targeted intracranial pharmacodelivery by modulating the BBB's receptivity to specific NCs [136] (Fig. 5).

4 Precision targeting and controlled action within the central nervous system microenvironment

Following successful traversal of the BBB, precise targeting of NCs to pathological lesions within the brain parenchyma is paramount for therapeutic success [137]. Uncontrolled or broad distribution of NCs throughout the brain can diminish therapeutic efficacy at the target site and increase the risk of off-target toxicities [26]. Consequently, achieving effective lesion targeting represents a critical subsequent step after BBB penetration. Researchers have primarily pursued two distinct strategic approaches to address this challenge: (1) harnessing unique aspects of the endogenous lesion microenvironment (e.g., altered pH, enzyme activity, redox potential, hypoxia) as intrinsic triggers for "smart", responsive NCs, leading to targeted drug release or functional modulation specifically at the lesion; and (2) employing external physical stimuli (e.g., magnetic fields, light, ultrasound, electric fields) to actively guide NCs, promote their accumulation, or trigger drug release selectively at the desired site. These strategies can be implemented independently or combined synergistically to enhance targeting precision and overall therapeutic efficiency.

4.1 Leveraging endogenous microenvironmental cues

The distinct pathophysiological microenvironments characteristic of many CNS disorders often deviate significantly from those found in healthy tissue. These endogenous differences present unique opportunities that can be exploited for targeted drug delivery. Stimuli-responsive NCs represent a sophisticated class of delivery systems specifically engineered to sense and react to these intrinsic pathological cues. This inherent responsiveness allows them to alter their physicochemical properties (e.g., size, charge, hydrophobicity) or functionality (e.g., drug release kinetics, cell penetration capacity), ideally leading to preferential accumulation and/or on-demand drug release precisely within the lesion microenvironment.

4.1.1 *pH-responsive systems*

pH-responsive NCs are designed to sense and react to the acidic microenvironments frequently encountered at diseased sites within the CNS, such as tumors or ischemic areas [138–142]. These carriers typically incorporate pH-sensitive chemical moieties (e.g., linkages susceptible to hydrolysis, ionizable groups undergoing protonation/deprotonation) or polymers that undergo

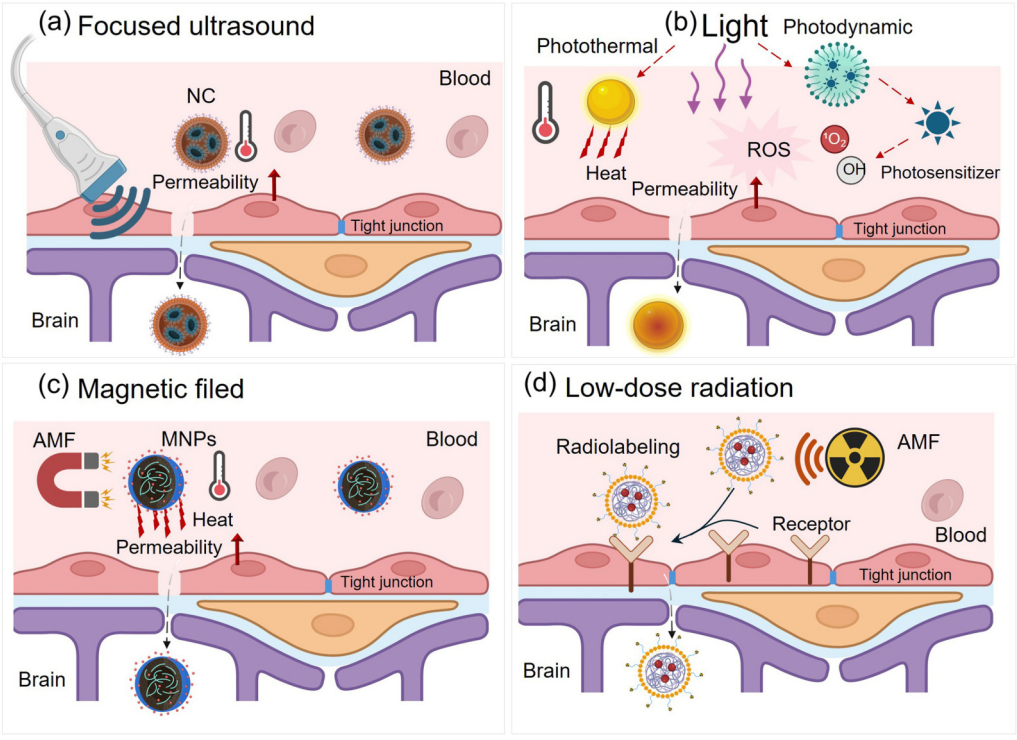

Figure 5 Physical strategies for enhancing nanocarrier transport across the blood-brain barrier. Physical approaches employed to transiently modulate BBB integrity and increase its permeability, facilitating the passage of circulating NCs into the brain parenchyma. (a) Focused ultrasound (FUS) application to a brain region. FUS induces mechanical effects that lead to temporary opening of tight junctions between endothelial cells, increasing BBB permeability and facilitating NC traversal. (b) Light-mediated methods. Photothermal therapy utilizes light-absorbing nanoparticles generating heat upon illumination, locally increasing temperature and enhancing BBB permeability. Photodynamic therapy involves photosensitizer-loaded nanoparticles producing ROS upon light exposure, disrupting endothelial cell junctions and increasing permeability. (c) Magnetic field application using an alternating magnetic field (AMF) applied externally to magnetic nanoparticles (MNPs) circulating in the bloodstream. AMF causes MNPs to generate local heat, leading to increased vascular permeability and facilitating the passage of MNPs and associated NCs across the BBB. (d) Low-dose radiation application, potentially with targeted nanocarriers (shown binding to endothelial receptors). Low-dose radiation transiently increases BBB permeability, aiding the transport of circulating nanocarriers into the brain. Receptor-mediated targeting can further enhance specific delivery.

conformational changes under acidic conditions. These triggered alterations modify the NCs' physicochemical properties or functionalities. By exploiting such pH variations, researchers have developed various pH-responsive NCs aimed at enhancing targeted drug delivery to CNS lesions.

For example, a pH-sensitive liposome incorporating a specific pH-responsive peptide was developed for improved targeting and therapeutic efficacy against glioblastoma [138]. This peptide reportedly conferred selective recognition of glioblastoma cells, guiding the liposomes specifically to the tumor site. The acidic tumor microenvironment then triggered a conformational change in the liposome, leading to doxorubicin release and, consequently, effective tumor cell killing. Similarly, supramolecular assemblies were designed for pH-triggered drug release specifically at lesion sites. Under the specific acidic conditions of the tumor microenvironment, these assemblies underwent structural alterations, initiating drug release and action precisely at the target site, thereby minimizing off-target effects in healthy tissues [143]. Further illustrating this lesion-specific approach, Graham-Gurysh et al. developed a pH-responsive polymeric platform for optimized paclitaxel delivery to glioblastoma. This polymer exhibited enhanced paclitaxel release within the acidic tumor environment, increasing local drug concentration at the lesion and reducing damage to surrounding healthy brain tissue [140].

The inherent targeting capabilities of pH-responsive NCs can be further augmented by integrating them with complementary targeting strategies, leading to enhanced precision and therapeutic efficacy. As an example, Sun et al. modified nanomicelles with the TfR-T12 peptide, for targeting TfR on tumor cell surfaces, and a pH-sensitive CPP to enhance cellular uptake within the acidic tumor microenvironment, thus achieving dual-targeted delivery [144]. Taking this combinatorial approach further, Martins et al. recently designed a multi-stimuli-responsive NC for docetaxel delivery, showcasing a sophisticated approach to lesion targeting [145]. The NC incorporated ANG2 for blood-brain barrier transcytosis and histidine for tumor cell internalization. A key feature of this design was the conjugation of ANG2 through a pH-sensitive linker, which underwent cleavage in the acidic endosomes of endothelial cells. This triggered a conformational change in the NC, exposing histidine and promoting targeted accumulation within the glioblastoma lesion. Consequently, this stimuli-responsive, multi-functional nanoplatform significantly improved chemotherapeutic efficacy against glioblastoma, offering a novel and effective therapeutic avenue (Fig. 6(a)).

4.1.2 *Enzyme-responsive systems*

The local microenvironment of many brain diseases exhibits significant alterations in the expression and activity levels of specific enzymes [146]. For instance, various proteases like matrix metalloproteinases, phosphatases, and glycosidases are often found at elevated levels in tumor tissues and inflamed areas within the brain [147]. This altered enzymatic landscape provides unique

opportunities for developing enzyme-responsive NCs, using these disease-associated enzymes not only as pathological markers but also as specific triggers for localized drug release or NC activation.

To achieve precise lesion targeting, enzyme-responsive NCs are typically engineered to incorporate enzyme-labile chemical bonds or motifs—such as specific peptide sequences, polysaccharide linkages, or ester bonds—either on their surface or within their core structure. Upon reaching the disease site where the target enzyme is overexpressed or hyperactive, the enzyme catalyzes the specific cleavage of these sensitive linkages or the modification of the incorporated groups. This enzymatic reaction, in turn, alters the physicochemical properties or functionality of the NCs, leading to controlled drug release, changes in solubility, cellular uptake, or other desired therapeutic actions [148]. Because enzymatic reactions can be highly specific and efficient, enzyme-responsive NCs offer a powerful mechanism for achieving precise therapeutic action specifically at the lesion, potentially minimizing off-target effects and maximizing efficacy [146, 148]

Capitalizing on enzyme-mediated activation, researchers have created a range of enzyme-responsive nanocarriers for treating brain diseases. A prime example exploited legumain overexpression, a characteristic feature of the glioblastoma microenvironment, to trigger the in situ aggregation of gold nanoparticles [149]. This strategically induced aggregation was shown to substantially increase nanoparticle retention within the brain tumor, directly enhancing lesion targeting. The NC employed in this study featured two distinct ligands: one designed to undergo legumain-catalyzed hydrolysis, exposing a 1,2-mercaptoamino group, and a second ligand capable of a click cycloaddition reaction with the newly exposed group. This enzyme-initiated reaction produced nanoparticle aggregates, effectively preventing their premature removal from the tumor. This case exemplifies how enzyme-responsive strategies can precisely control nanoparticle localization and behavior within target tissues.

Matrix metalloproteinase-2 (MMP-2)-sensitive peptides also represent a valuable tool in designing enzyme-responsive NCs for brain targeting. An MMP-2-responsive NC, termed S-biAb/dEGCG@NPs, was developed for glioblastoma therapy [150]. This NC comprised a recombinant anti-B7-H3×CD3 bispecific antibody (biAb) and a ferroptosis enhancer, dimeric EGCG (dEGCG). To achieve targeted release, the nanocarrier surface was functionalized with an MMP-2-sensitive peptide linker. This peptide was selectively cleaved within the MMP-2-rich microenvironment of the glioblastoma, liberating the therapeutic payload precisely at the tumor site. The released dEGCG reportedly potentiated interferon-γ (IFN-γ)-induced ferroptosis, leading to tumor cell membrane disruption and the subsequent release of tumor-associated antigens. This antigen release was proposed to create a synergistic effect with biAb-mediated T cell activation, significantly enhancing the response to immune checkpoint blockade (ICB) therapy in preclinical models (Fig. 6(b)).

4.1.3 ROS-responsive systems

ROS are natural byproducts of cellular metabolism. However, in numerous brain pathologies, an imbalance between ROS production and endogenous antioxidant defenses leads to oxidative stress, which significantly contributes to disease progression. For example, in brain tumors like glioblastoma, factors including mitochondrial dysfunction, chronic inflammation, and altered metabolism result in markedly elevated intracellular and extracellular ROS levels. Ischemic stroke is characterized by a burst of ROS production, particularly during the reperfusion phase, which exacerbates neuronal damage and compromises BBB integrity. Similarly, in Alzheimer's disease, the accumulation of Aβ, metal ion dyshomeostasis, and mitochondrial dysfunction are known to elevate ROS levels, fostering neuronal apoptosis and cognitive decline. This disease-specific upregulation of ROS serves as a critical endogenous stimulus for the design and application of ROS-responsive NCs.

Engineered to target areas of heightened oxidative stress, ROS-responsive NCs are designed to selectively react with the high concentrations of specific ROS (e.g., H_2O_2, ·OH, $ONOO^-$) found at diseased sites within the brain. This interaction triggers the oxidative cleavage or structural transformation of ROS-sensitive chemical bonds or moieties incorporated within the NC structure. Consequently, this can lead to controlled effects such as NC disassembly, payload release, particle swelling, surface charge reversal, or altered hydrophobicity [151]. By leveraging both the disease-specific increase in ROS and the responsiveness of these NCs, researchers have created a variety of NCs for targeted therapy and theranostics in brain diseases.

To improve therapeutic outcomes against highly invasive and treatment-resistant glioblastoma, researchers have focused on developing ROS-responsive nanocarriers that enhance lesion targeting through various mechanisms. One key strategy is ROS-triggered drug release, enabling precise drug delivery to the tumor site. A polymer-siRNA complex modified with thioether bonds, for example, was engineered to release gene therapeutics selectively within the elevated ROS environment of the glioblastoma, leading to the silencing of VEGF and c-Myc and, consequently, the inhibition of tumor growth and angiogenesis [152]. Enhancing tumor penetration is another important goal. Hyperbranched polyphosphate NPs that underwent a ROS-induced size reduction (from ~ 100 to ~ 20 nm) were shown to facilitate deeper distribution within the tumor mass [153]. Dual-targeting strategies offer further precision. NCs modified with Angiopep-2/T7 dual peptides for enhanced BBB/tumor cell targeting, combined with ROS-triggered siRNA release for dual-gene silencing, were developed for immunochemotherapy [154].

In the context of ischemic stroke, ROS-responsive nanocarriers are being developed to leverage synergistic mechanisms for neuroprotection and functional recovery. Cerium oxide NPs (CeNPs) exemplify a sophisticated design for targeted action [155]. These CeNPs featured a CeO_2 core that continuously scavenged ROS via the Ce^{3+}/Ce^{4+} redox cycle, providing intrinsic antioxidant activity and protecting the loaded payload. Simultaneously, the free radical scavenger edaravone was loaded onto the NP surface for controlled release during and after BBB transit. This strategically timed release was proposed to complement the CeO_2 core's activity, establishing a "protection-during-transcytosis" effect. By neutralizing ROS along their path across the compromised BBB, the CeNPs reportedly minimized ischemia-reperfusion injury to the barrier itself, thereby enhancing edaravone delivery to the ischemic penumbra. Extending this concept, a polydopamine (PDA)-based nanosystem employed a sophisticated, staged-release strategy responding to the evolving stroke pathophysiology [156]. This system leveraged the inherent free radical scavenging ability of PDA for initial antioxidant protection during the acute phase of high ROS. Subsequently, as the disease progressed to an inflammatory stage characterized by elevated MMP-2 levels, the nanosystem responded by releasing loaded minocycline, an anti-inflammatory

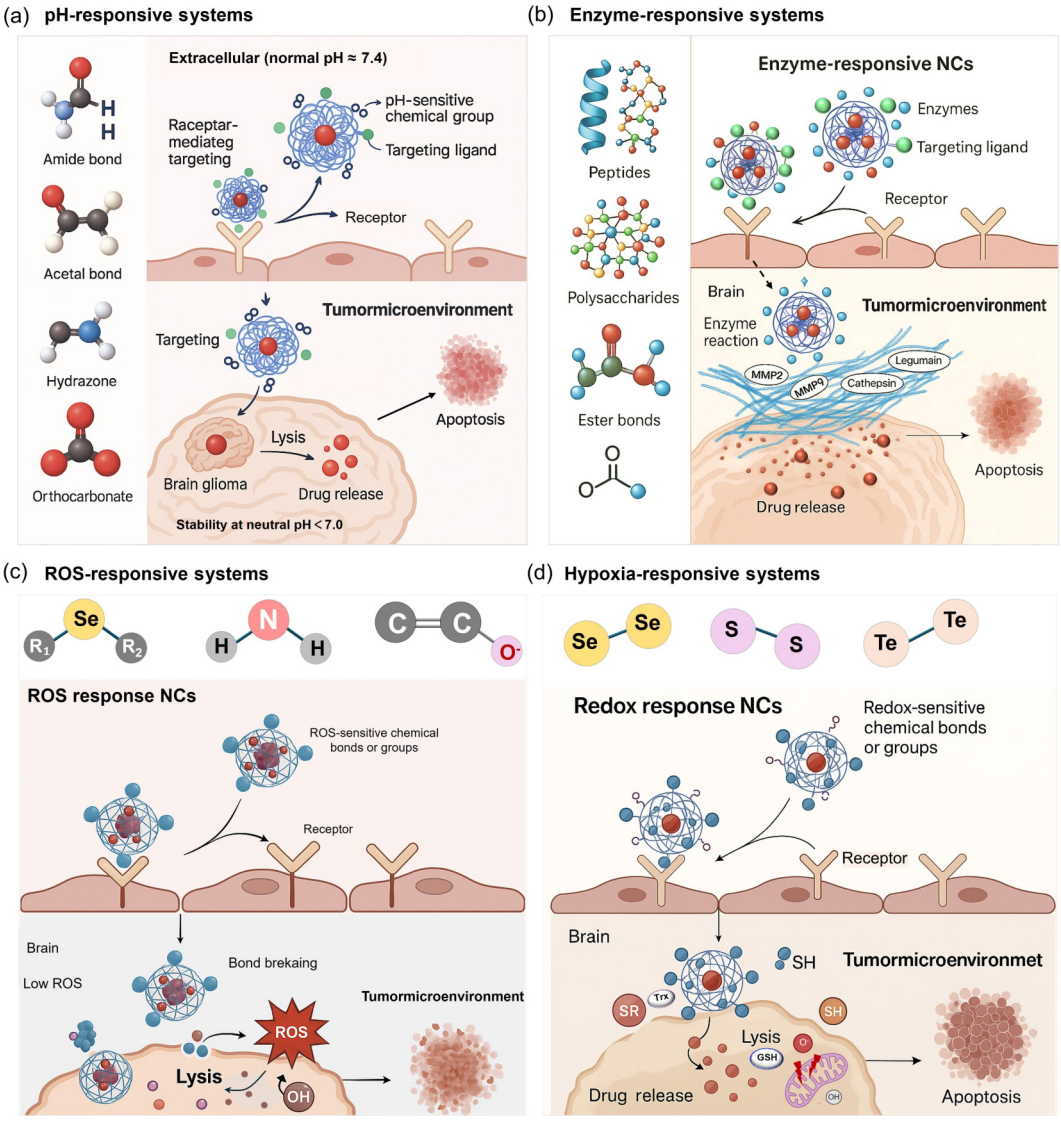

Figure 6 Endogenous microenvironmental cues for precision targeting and triggered drug release. This figure illustrates the design principles and mechanisms of nanocarriers engineered to respond to specific endogenous microenvironmental cues (pH, enzymes, reactive oxygen species, and redox potential) for precise drug delivery and triggered release within brain tumors. (a) pH-responsive systems: The left side presents common pH-sensitive chemical linkages (amide bond, acetal bond, hydrazone, orthocarbonate) that confer pH responsiveness. The top right panel depicts nanocarriers (purple/red sphere with blue targeting ligands) circulating extracellularly (at physiological pH ≈ 7.4). These NCs bind to receptors (brown Y-shaped proteins) on the BBB endothelium, facilitating receptor-mediated transcytosis into the brain parenchyma (where pH ≈ 7.0). Stability is maintained at neutral pH, preventing premature drug release. The lower right panel illustrates the nanoparticle within the acidic brain glioma tumor microenvironment (pH < 7.0). Upon encountering this lower pH, the pH-sensitive chemical groups undergo cleavage or conformational changes, leading to nanoparticle lysis and controlled release of the encapsulated drug cargo (red spheres), resulting in tumor cell apoptosis. (b) Enzyme-responsive systems: The left side presents molecular structures representing materials and chemical linkages (peptides, polysaccharides, ester bonds) for imparting enzyme sensitivity to nanoparticles. The right panel depicts the nanoparticle system functionalized with targeting ligands (turquoise spheres) binding to receptors (brown Y-shaped proteins) on the BBB endothelium, facilitating receptor-mediated transcytosis into the brain parenchyma. Within the brain tumor microenvironment, characterized by elevated enzyme levels (e.g., MMP2, MMP9, Cathepsin, Legumain, represented by oval shapes), enzyme-responsive components are cleaved or modified. This enzyme-catalyzed degradation or disassembly of the nanoparticle results in controlled release of encapsulated drug cargo directly at the tumor site, leading to tumor cell apoptosis. (c) ROS-responsive systems: The top panel presents chemical structures representing common ROS-sensitive chemical linkages or groups (e.g., organoselenium, amine, vinyl ether) for conferring responsiveness to oxidative stress. The middle section depicts the nanoparticle system (purple/red sphere with blue targeting ligands) circulating in the bloodstream, with ligands binding to receptors (brown Y-shaped proteins) on the BBB endothelium, facilitating receptor-mediated transcytosis into the brain parenchyma (low ROS environment). The bottom section illustrates the nanoparticle within the brain tumor microenvironment, characterized by significantly higher ROS levels. Upon encountering this oxidative environment, ROS-sensitive bonds or groups undergo cleavage, leading to nanoparticle lysis and controlled release of encapsulated drug cargo (red spheres) directly at the tumor site, inducing tumor cell apoptosis (represented by cell clustering). (d) Redox-responsive systems: The top panel presents common redox-sensitive chemical linkages (disulfide (S–S), diselenide (Se–Se), ditelluride (Te–Te) bonds) for conferring responsiveness to redox potential changes. The nanoparticle system (purple/red sphere with blue targeting ligands) circulates in the bloodstream, targeting receptors (brown Y-shaped proteins) on the BBB endothelium for receptor-mediated transcytosis into the brain parenchyma (low reduction environment). The brain tumor microenvironment features a significantly higher concentration of reducing agents ("high reduction environment") compared to healthy tissue. Within a tumor cell (bottom section), high levels of reducing agents like Glutathione (GSH) and Thioredoxin (Trx) (oval shapes) cleave the redox-sensitive bonds, leading to nanoparticle lysis, controlled release of encapsulated drug cargo (red spheres) at the tumor site, and tumor cell apoptosis (cell clustering).

agent. This MMP-2-triggered release was shown to inhibit microglial overactivation and mitigate the pro-inflammatory microenvironment.

Turning to Alzheimer's disease (AD), researchers have designed "smart" NCs that capitalize on the high ROS levels characteristic of the AD brain. These systems often utilize ROS-sensitive chemical linkers, such as thioketals, to conjugate or encapsulate therapeutic cargo. For example, one study created dual-gene nanovesicles employing a thioketal linker [157]. This linker connected siRNA (to reduce Aβ production) and BDNF mRNA (to promote neuronal survival). In the high-ROS AD environment, the linker was designed to break, co-releasing both genetic payloads precisely at the site of pathology. Building upon this, researchers have combined ROS sensitivity with theranostic capabilities. A novel brain-targeting, ROS-responsive nanoplatform (Ang-AIE NCs) was created, utilizing two specialized aggregation-induced emission luminogens (AIEgens) within hydrophilic nanocomposites [158]. These nanocomposites displayed an extended *in vivo* half-life and achieved unprecedented 1350 nm NIR-II imaging sensitivity, enabling transcranial monitoring of Aβ plaques. Critically, the Ang-AIE NCs leveraged the elevated ROS levels in the AD brain for targeted therapeutic action. The inflammatory microenvironment triggered the release of the AIEgens, initiating a synergistic therapeutic effect: one AIEgen component directly disrupted Aβ fibrils and disassembled existing plaques, while the other, featuring a Ce(III) center, actively scavenged ROS, thereby mitigating further Aβ formation and preventing reaggregation. This multifunctional nanocarrier, through its ROS-mediated targeting, Aβ degradation, and NIR-II imaging capabilities, facilitated precise AD theranostics. This "dual-pronged" approach reportedly created a self-reinforcing cycle, leading to significant cognitive improvement in AD model mice (Fig. 6(c)).

4.1.4 *Hypoxia-responsive systems*

Hypoxia is a hallmark pathological feature in numerous brain diseases. In brain tumors, particularly glioblastoma, the confluence of rapid cell proliferation, aberrant vasculature, and inadequate angiogenesis creates a characteristic hypoxic microenvironment. Similarly, ischemic stroke precipitates localized cerebral ischemia and hypoxia due to vascular occlusion, initiating a cascade of detrimental events. Exploiting this commonality, hypoxia-responsive nanocarriers have emerged as a class of 'smart' delivery systems engineered for hypoxia-specific activation and targeted delivery within hypoxic lesions [159–162].

Azobenzene groups, for instance, have been incorporated into liposomal NCs for brain tumor therapy. Within the hypoxic tumor core, these azobenzene groups were shown to undergo chemical reduction. This reduction reaction altered the liposome's structure, causing payload release (e.g., siRNA) and potentially enhancing cellular uptake [159, 161]. A prime example is a NC that, triggered by the low-oxygen environment, released both the chemotherapeutic drug doxorubicin (DOX) and the photosensitizer chlorin e6 (Ce6). Subsequent near-infrared irradiation activated the Ce6 to produce ROS for photodynamic therapy, while a co-loaded DiR dye enabled fluorescence-guided surgery, illustrating the potential for multi-modal treatment enhancement through hypoxia targeting [159].

Alternatively, hypoxia targeting can exploit the hypoxia-induced upregulation of specific receptors within the lesion. A pertinent example involved the self-assembled HSAP-NP developed for stroke therapy, which incorporated the receptor for advanced glycation end products (RAGE)-binding peptide HSAP and a therapeutic gene (pHO1) [160]. Since the RAGE became highly expressed in the hypoxic ischemic area, the HSAP peptide facilitated preferential NP accumulation at the lesion via receptor binding, while simultaneously offering cytoprotection by inhibiting deleterious RAGE signaling. This dual-function approach reportedly boosted gene delivery efficiency within the ischemic region and reduced infarct volume in stroke models, showcasing the utility of targeting hypoxia-induced molecular signatures (Fig. 6(d)).

4.1.5 *Electric-responsive systems*

Epilepsy is characterized by aberrant electrical activity within the brain. During epileptic seizures, neurons fire in an abnormally synchronized manner, causing significant alterations in the local electric field. These alterations manifest as atypical brainwave patterns—such as spikes, sharp waves, and spike-and-wave complexes—and pronounced fluctuations in local electrical potentials. These aberrant electrophysiological events are not only hallmarks of epilepsy for diagnosis, but also serve as unique "trigger signals" for the development of electric-responsive nanocarriers.

A recent study introduced a nanocarrier composed of polypyrrole (PPY) and polydopamine (PDA), exhibiting a 125-fold increase in conductivity over pure PPY [163]. This allowed for drug release in response to an extremely weak electrical stimulus (as low as 50 μA). The carrier's high conductivity enabled real-time detection of the aberrant neuronal discharges of epileptic seizures, triggering the release of phenytoin sodium within 30 s. Additionally, a polydopamine-modified Angiopep-2 peptide targeted the LRP1 receptor on the blood-brain barrier (BBB), increasing brain drug concentrations five-fold compared to conventional methods. The study also incorporated a near-infrared photothermal effect to reversibly modulate BBB permeability via localized heating, creating an "electric field response—active targeting—photothermal assistance" multimodal synergy. In animal models, this strategy not only reduced seizure frequency by 82% but also lessened the toxicity associated with conventional carriers. This represents a significant advance over traditional drug delivery, which often relies on high-threshold stimulation, and addresses therapeutic delay, paving the way for on-demand epilepsy treatment.

Beyond single-stimulus responsiveness, electric sensitivity can be integrated with other response modalities to create even more sophisticated drug delivery systems. As an example, another study developed a ROS/electro dual-responsive nanogel [164]. This nanogel is strategically designed with three key components: a ROS-responsive phenytoin (PHT) prodrug, an electro-responsive group (sulfonate sodium, SS), and an epileptic foci-recognizing group (α-methyl-l-tryptophan, AMT). This multi-component structure enables targeted accumulation at seizure sites, followed by ROS-triggered PHT release, inhibition of overexcited neuronal circuits, and a reduction in oxidative stress and inflammation. The result is a comprehensive and synergistic approach to epilepsy therapy (Fig. 7(a)).

4.1.6 *Chemotaxis-responsive systems*

Brain disorders are frequently accompanied by localized, and often intense, inflammatory responses during their progression. A key feature of this inflammation is the substantial release of chemokines (e.g., CCL2, CX3CL1, CXCL2) by resident brain cells or infiltrating immune cells, which establishes chemotactic gradients within the

affected tissue. Inspired by this natural process, researchers have engineered a novel class of targeted NCs that exploit chemotactic principles, typically by using cell membrane coating technology. These NCs are cloaked in the membranes derived from specific cell types (e.g., neutrophils, macrophages, stem cells), thereby imbuing the NPs with the chemotactic migration capabilities inherent to the parent cells due to the presence of functional chemokine receptors on the membrane surface.

For example, NPs coated with neutrophil membranes, which naturally express receptors for various inflammatory chemokines and relevant adhesion molecules, exhibited directed migration towards the ischemic region in preclinical stroke models in response to inflammatory signals [165]. Similarly, NPs functionalized with macrophage or neutrophil membranes were shown to leverage their endogenous chemokine receptors (e.g., for CCL2, CX3CL1) to respond to chemotactic cues emanating from the glioblastoma microenvironment, achieving active tumor targeting [166, 167]. In AD models, NCs coated with hybrid cell membranes- composed of a platelet membrane fused with a membrane from cells engineered to overexpress the chemokine receptor CCR2- were able to respond to CCL2 released by activated microglia and astrocytes, thereby enabling targeted delivery to inflammatory lesions[168]. In essence, these cell membrane-coated NCs, by virtue of their preserved chemokine receptors and resulting sensitivity to chemotactic gradients, offer a "smart", biomimetic targeting strategy that mimics natural cellular homing mechanisms for the precision treatment of various brain diseases (Fig. 7(b)).

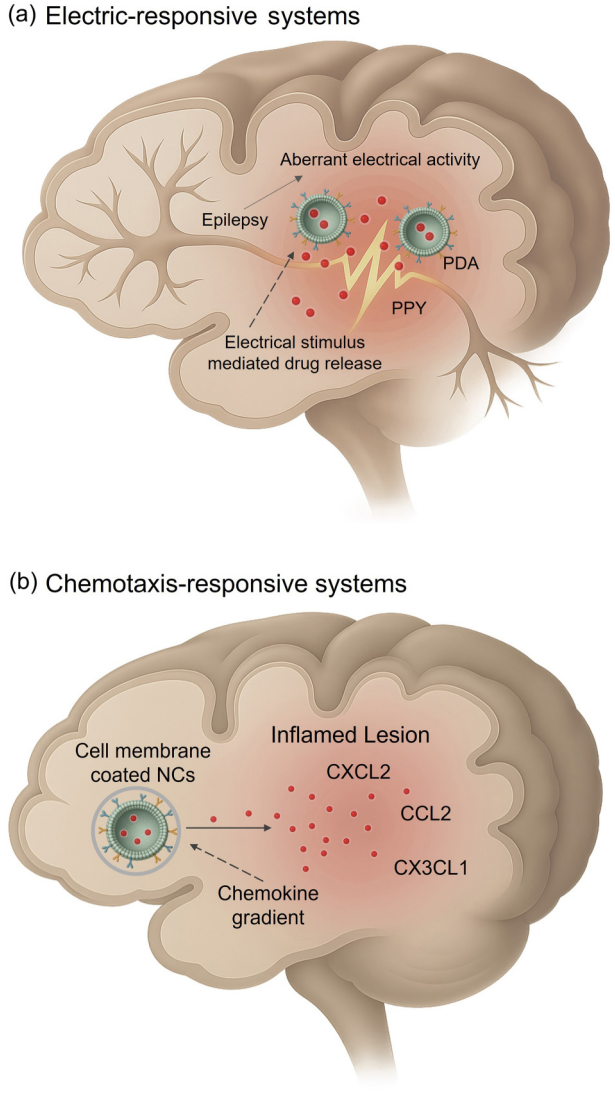

Figure 7 Exogenous stimuli-guided nanocarrier delivery and cell-specific action. This figure illustrates physical strategies employed for precise targeting and controlled action of nanocarriers within the brain parenchyma following BBB traversal, leveraging external stimuli like electric fields and chemotactic gradients.

(a) Electric field-responsive nanocarrier systems for targeting regions of abnormal electrical activity in the brain. Brain tissue depicting neurons and a region characterized by heightened or pathological electrical signaling (lightning bolt, radiating field). Engineered electric field-responsive nanocarriers (blue spheres with lightning bolt icons, loaded with red spheres representing drug payload) circulate in the brain parenchyma. These nanocarriers are designed to alter their properties or release encapsulated drug payload in response to localized electrical signals. Upon encountering the region of aberrant electrical activity (e.g., Epilepsy), the electric field triggers controlled release specifically at the site, leveraging intrinsic pathological electrical cues for precise, localized drug delivery. Examples like PPY and PDA-based nanocarriers are shown.

(b) Chemotaxis-responsive nanocarrier systems for targeting inflamed brain lesions. This figure illustrates the concept of utilizing chemotaxis for targeted drug delivery to inflamed regions within the brain tissue. Inflamed lesions, such as the one depicted, release signaling molecules known as chemokines (represented by small blue spheres), which establish a concentration gradient within the surrounding brain parenchyma. Examples of relevant chemokines, such as CCL2, CXCL2, and CX3CL1, are shown diffusing from the lesion, creating a chemokine gradient. Cell membrane-coated nanocarriers (depicted at the bottom left) are engineered to respond to these chemokine gradients. The properties conferred by the cell membrane coating enable these nanocarriers to exhibit chemotaxis, directing their movement towards the higher concentration of chemokines at the site of inflammation. This chemokine-guided migration facilitates the targeted accumulation of nanocarriers specifically within the inflamed lesion, enhancing the potential for local therapeutic intervention.

4.2 Exogenous stimuli-guided delivery and triggered action

Beyond facilitating the initial translocation of nanocarriers (NCs) across the blood-brain barrier (as discussed in Section 3.5), exogenous physical stimuli offer a critical pathway for enhancing the precision of nanoparticle delivery and therapeutic action within the brain parenchyma following BBB traversal. These approaches differ from strategies that merely permeabilize the BBB. Instead, they use external stimuli to actively control engineered NCs after they have entered the brain. This control can either guide the NCs to pathological lesions or trigger on-demand therapeutic responses directly within the disease microenvironment. This synergistic combination of externally guided targeting and stimulus-triggered internal responsiveness holds immense potential for maximizing drug accumulation and therapeutic efficacy at the target site while minimizing systemic exposure and off-target toxicity. Various external stimuli, including focused ultrasound (FUS), light, magnetic fields, and low-dose radiation, have been ingeniously integrated into the design of functional nanoparticle systems to achieve these capabilities. FUS, a versatile, non-invasive stimulus, has been

explored for triggering on-demand drug release from appropriately designed NCs within brain tumors, enhancing local drug concentrations and therapeutic effect against glioblastoma [117]. Recent advances have helped elucidate synergistic mechanisms, such as microbubble-enhanced ultrasound amplifying tumor-targeting capability of cationic lipid NPs and enhancing interstitial fluid flow to promote NP dispersion and transfection efficiency within tumor tissue [120, 169]. Beyond triggered release, FUS can also induce piezoelectric effects in specialized nanomaterials like hybrid lipid-polymer piezoelectric NPs (PNPs) [170] or layered MoS_2 nanosheets [171], converting mechanical energy into localized electrical stimulation to modulate cellular activity, influence tumor cell migration/invasion, activate intracellular pathways, or enhance drug uptake. FUS-mediated drug release from engineered nanoemulsions has also enabled targeted neuromodulation in models of neurological disorders like epilepsy [172]. Precision and safety of FUS-based therapies are often enhanced by integration with imaging modalities like MRI for precise localization and real-time monitoring [120, 121], allowing synergistic combinations, such as magnetically guided NCs followed by FUS to enhance drug diffusion and locally activate receptors for treating intracerebral hemorrhage [171]. Light-based approaches, particularly utilizing external illumination, have increasingly focused on photothermal therapy (PTT) and photodynamic therapy (PDT) in brain tumor therapy. Engineered nanoparticle systems incorporating photothermal agents [173, 174] [175, 176] or photosensitizers [129] are designed for efficient conversion of light energy into localized heat or cytotoxic ROS, respectively, often integrated with targeting ligands for enhanced specificity [173] or cell membrane coating for homotypic targeting [174]. Multimodal light-responsive nanoplatforms enabling deep tissue-penetrating thermal ablation under NIR-II laser irradiation and real-time imaging [175, 176] have also been developed. Through ingenious NC design, PTT and PDT can be combined for potential synergistic effects [130, 131], leveraging mechanisms like Förster resonance energy transfer (FRET) to maximize energy transfer and achieve highly effective synergistic therapy for glioma ablation [130]. Future NC designs trend towards integrating multiple targeting and response mechanisms for precise theranostics, utilizing strategies like molecular co-assembly responsive to tumor microenvironment cues to release drug payloads and photosensitizers for synergistic chemo-photodynamic therapy under image guidance [177]. Magnetic field-guided strategies leverage the interaction between magnetic NPs and externally applied magnetic fields to achieve precise targeting within the brain. Engineered magnetic nanoparticles, often associated with therapeutic agents, are actively guided by an external magnetic field gradient to accumulate preferentially at targeted brain regions, significantly increasing local drug concentration and therapeutic efficacy while reducing damage to surrounding healthy tissue [133, 178, 179]. This strategy's efficacy stems from a sophisticated understanding and modulation of the NPs' *in vivo* behavior. For instance, MNP-mediated magnetic fluid hyperthermia (MFH) not only selectively heats target sites but also alters BBB permeability, a key mechanism that enhances drug delivery [180]. Beyond simple guidance, magnetoelectric NPs (MENs) can convert magnetic energy into localized electrical stimulation to modulate neuronal activity [181]. Magnetic guidance has also been employed to deliver complex biological cargo, such as mitochondrial donors integrated with magnetic NPs for targeted delivery to support cellular function and promote functional recovery after intracerebral hemorrhage [182]. Magnetic fields can be combined with other functionalities, such as thermosensitive magnetic NCs designed for magnetic hyperthermia-triggered drug release under an alternating magnetic field (AMF) [183]. Magnetic NPs often serve as contrast agents for MRI [184], and when combined with targeting ligands, they enhance lesion visualization and guide delivery, offering multimodal imaging capabilities for diagnosis and real-time surgical guidance [185, 186]. Low-dose radiation has been explored to modulate the brain microenvironment, enhancing active targeting and improving lesion targeting in glioblastoma treatment. This approach leverages low-dose radiotherapy specifically applied to the tumor site to enhance the migration of monocyte-delivered nanoparticles ("hitchhiking") [187] or boost the accumulation of targeted nanoparticles within the brain tumor, leading to more effective drug or gene silencing. Furthermore, ingenious nanomaterial design can be synergistically integrated with the spatiotemporal characteristics of radiotherapy to optimize therapeutic outcomes. Examples include selenium-engineered mesoporous silica nanocapsules (Se-MSN) that undergo controlled degradation upon low-dose X-ray exposure to release therapeutic payloads and simultaneously activate radiosensitizing agents in the hypoxic microenvironment, amplifying DNA damage and enhancing radiation sensitivity [188, 189]. These strategies underscore the potential of leveraging low-dose radiation to improve nanoparticle delivery and therapeutic response in brain lesions.

5 Intra-lesional cell-specific targeting: Precision delivery in the brain

After achieving successful accumulation of NCs within the targeted brain lesion, the subsequent critical step towards realizing precise therapy involves engaging specific cell types within that lesion. The microenvironment of brain lesions presents a complex, heterogeneous milieu comprising diverse cell populations, rather than a uniform target. Glioblastoma, for instance, involves not only tumor cells but also significant numbers of tumor-associated macrophages (TAMs), endothelial cells, astrocytes, and other stromal cells. Similarly, lesions in AD are characterized by intricate interactions between neurons, activated microglia, reactive astrocytes, and other cell types. Consequently, non-specific drug delivery to the lesion site often yields suboptimal efficacy and can cause adverse effects by acting indiscriminately on various cell types, including healthy bystander cells. To enhance precision, maximize efficacy, and minimize off-target toxicity, strategies must advance from lesion-level to cell-specific targeting, enabling recognition and functional interaction with distinct cell populations.

5.1 Physicochemical property-mediated targeting

The intrinsic physicochemical properties of NCs, including size, shape, and surface characteristics (charge and chemistry), play a crucial role in modulating their interactions with different cell types within the brain, potentially conferring a degree of passive cell selectivity.

First, particle size is a critical parameter influencing cellular uptake pathways and targeting behavior, often exhibiting cell-type dependencies. This size influence was evident across various cell and NP types. For example, studies involving gold NPs showed that neuronal uptake was size-dependent: smaller particles (~ 15 nm) reportedly favored uptake by undifferentiated neurons, whereas

larger particles (~ 40 nm) were preferentially internalized by differentiated neurons [190]. Similarly, activated glial cells, known for enhanced phagocytic activity in CNS disease states, were effectively targeted by densely-packed, hydroxyl-functionalized, PEG-modified dendrimers falling within a specific size range (~ 4–5 nm) [191]. Further supporting the significance of size, investigations using mesoporous MSNs indicated that smaller MSNs (~ 50 nm) were more readily taken up by glioma cells, leading to improved anti-tumor efficacy compared to their larger counterparts (~ 100 and 200 nm) [192]. These diverse examples underscore that careful control over NC size is essential for optimizing cell-specific interactions within the brain.

Second, the shape or morphology of NCs also significantly influences their cellular interactions. Different nanomaterial geometries, including nanoscaffolds, nanotubes, nanowires, and nanocones, were shown to differentially affect neuronal processes such as regeneration, differentiation, and survival rates [193]. This shape-dependent interaction was particularly evident with microglia, the brain's primary phagocytes. Microglia demonstrated a clear preference for certain shapes; for instance, they more readily internalized spiky, sea urchin-like particles compared to spherical or rod-shaped NCs [194–196].

Beyond size and shape, the surface charge of NCs is another critical physicochemical property profoundly influencing interactions with cell membranes. Studies employing neuron-glia co-culture systems demonstrated that negatively charged NPs exhibited a significantly higher selective affinity for neuronal cell membranes compared to positively charged or neutral NPs [197]. This preference was also observed for other nanomaterials; for instance, negatively charged quantum dots were reported to be more selectively internalized by neurons [198].

However, delving deeper than overall surface charge, the detailed chemical composition of NCs emerges as a critical factor in dictating cell-specific targeting within the brain. This includes both specific chemical groups presented on the NC surface and the nature of the materials comprising the NC core. For instance, dendrimers engineered with abundant surface hydroxyl groups were shown to selectively target activated microglia/macrophages, demonstrating how specific surface chemistry drove these interactions [191]. Similarly, optimizing the core chemical makeup of lipid NPs (LNPs), specifically by varying the constituent ionizable lipid, led to formulations preferentially taken up by microglia *in vitro* and *in vivo* [199]. These examples underscore that the NC's chemical identity, whether defined by specific surface functionalities or the collective properties arising from its core components, can be precisely engineered to achieve preferential uptake by distinct brain cell populations, often without relying on traditional targeting ligands. Collectively, these diverse examples emphasize that careful engineering and control over fundamental NC physicochemical properties are essential considerations for optimizing cell-specific interactions and targeting within the complex cellular landscape of the brain.

5.2 Surface functionalization-mediated targeting

To achieve more precise drug delivery to designated cell types within the brain, researchers have actively explored various active targeting strategies. These primarily rely on specific, high-affinity interactions between targeting ligands conjugated onto the NC surface and cognate cell surface markers or receptors uniquely or predominantly expressed on the target cell population.

Effective strategies have been developed for targeting astrocytes. These included utilizing arginine-rich polymeric systems for gene delivery to primary human astrocytes [198, 200] and employing lipopolysaccharide (LPS)-functionalized NPs to specifically engage reactive astrocytes in spinal cord injury models [201]. Furthermore, various ligands conjugated onto NCs, such as the triphenylphosphonium cation (TPP) [202], the reactive astrocyte-specific homing peptide (AS1) [203], and the peptide gH625 [5], proved effective in achieving preferential delivery to astrocytes in different contexts.

Targeting neurons remains a major research focus, frequently accomplished by functionalizing NPs with specific peptides. A prominent example is the rabies virus glycoprotein (RVG) peptide. RVG-modified NPs specifically bound neurons *in vivo* [204] and successfully delivered therapies to dopaminergic neurons in Parkinson's disease models [205]. Another key ligand is the tetanus toxin-derived Tet-1 peptide, which displayed high affinity for motor neurons through interactions with gangliosides [206]. Conjugating Tet-1 to various NPs facilitated efficient therapeutic delivery [207], an effect often amplified by co-functionalization with BBB-targeting peptides [177, 208, 209]. Engineered fusion peptides, such as TPL linking Tet-1 and the BBB-penetrating peptide TGN, were designed to offer superior stability, flexibility, and dual targeting capabilities compared to mixtures of separate peptides. Exemplifying this, a TPL-modified nano-dredger delivered siROCK2/LA, reportedly restoring axonal autophagy in AD models and highlighting the potential of engineered peptides [210]. Furthermore, endogenous ligands involved in neuronal homeostasis, including nerve growth factor (NGF), dopamine, transferrin, and lactoferrin, have been utilized to guide NCs to neurons [211–213]. A notable application targeted the upregulation of fibroblast growth factor receptor (FGFR1) observed on cholinergic neurons in AD [214]. By functionalizing NPs with FGF ligands, researchers delivered combined antioxidants and neuroprotective peptides, successfully ameliorating mitochondrial stress within these specific neurons and achieving significant physiological and functional improvements in AD mouse models.

While microglia's inherent phagocytic nature facilitates the uptake of various materials, active targeting strategies offer enhanced efficiency and specificity. For instance, ceria-zirconia NPs functionalized with CD11b antibodies showed markedly increased internalization by microglia in mouse models of neuropathic pain [215].

While microglia's inherent phagocytic capabilities facilitate the uptake of materials, active targeting strategies offer enhanced efficiency and specificity for delivery. For instance, ceria-zirconia nanoparticles functionalized with CD11b antibodies showed markedly increased internalization by microglia in mouse models of neuropathic pain Similarly, liposomes modified with lipopolysaccharide (LPS) were selectively taken up by microglia through targeting Toll-like receptor 4 (TLR4), which helped delay disease progression. Furthermore, screening lipid nanoparticle (LNP) libraries led to the identification of a microglia-specific LNP (MG-LNP) that effectively delivered siRNA targeting the PU.1 gene in mouse models of chronic neuroinflammation.

Directly targeting brain tumor cells is a key strategy for improving treatment outcomes. Since brain tumor cells frequently overexpress specific surface markers like the epidermal growth factor receptor (EGFR) [216], these molecules provide valuable targets for ligand-functionalized NCs. Notably, several prominent

targets utilized for tumor cell engagement, such as the transferrin receptor (TfR) [217–222], integrin αvβ3 [223–227], and the folate receptor [228], also play roles in mediating NC transport across the BBB (as discussed previously). This potential dual functionality offers a synergistic advantage, possibly facilitating enhanced drug accumulation within the target tumor cells after BBB transit.

As crucial components of the tumor microenvironment, TAMs are also important targets for active delivery strategies. Although TAMs share similarities with resident microglia, they often express distinct markers suitable for targeting. For example, p-aminophenyl-α-D-mannopyranoside (MAN) can target the macrophage mannose receptor (MMR). One study developed a sophisticated delivery system using MAN to target TAMs in glioblastoma [229]. This system cleverly used the enzyme cathepsin B (CTSB), abundant in the tumor microenvironment, to trigger the exposure of a MAN ligand, which then specifically targeted the MMR on TAMs. Such targeted delivery reportedly effectively reprogrammed TAMs towards an anti-tumor M1 phenotype, significantly boosting therapeutic efficacy. Other peptide ligands also effectively targeted specific TAM populations. The M2-specific peptide (M2pep), for example, actively bound surface markers on M2-polarized TAMs, thereby improving MRI nanoprobe accumulation within these cells [230]. Likewise, the KDKPPR peptide targeted the Neuropilin-1 (NRP-1) receptor, known to be upregulated on M2 TAMs in glioblastoma. Functionalizing AGuIX® NPs with KDKPPR resulted in a threefold increase in uptake by M2 versus M1 macrophages, highlighting a viable strategy for delivering agents like PDT photosensitizers specifically to TAMs [128].

5.3 Cell membrane-mediated targeting

Cell membrane-coated NPs (CMCNPs) are engineered by isolating membranes from specific source cells, such as tumor cells, immune cells, or stem cells, and cloaking them onto the surface of NC cores. This process allows CMCNPs to retain a diverse array of biomolecules native to the source cell membrane, including membrane proteins, lipids, and glycans. Consequently, these biomimetic NPs inherit unique biological functionalities and targeting capabilities derived directly from the source cell.

For brain tumor treatment, cancer cell membrane-coated NPs (CCMCNPs) offer significant advantages through inherent homotypic targeting. CCMCNPs can selectively bind to tumor cells of the same origin because they retain native adhesion molecules and surface receptors that mediate these specific cell-cell interactions. As an example, coating doxorubicin-manganese dioxide NPs with C6 glioma cell membranes reportedly achieved precise targeting towards glioma cells [231].

To further improve targeting precision and therapeutic outcomes, researchers have optimized CCMCNPs using several strategies. One approach involved functional modification, such as incorporating the cRGD peptide onto the membrane surface [232]. While preserving the membrane's potential immune-cloaking properties, this strategy leveraged cRGD's specific binding to αvβ3 integrin to boost targeting tumor cells. A more advanced strategy employed cross-scale biomimicry, exemplified by Gboxin nanodrugs coated with engineered tumor cell-mitochondria hybrid membranes [233]. Here, fusing tumor cell and mitochondrial membranes endowed the carrier with dual targeting capabilities: tumor cell membrane components mediated BBB transit and tumor homing, while specific mitochondrial proteins guided intracellular delivery and precise mitochondrial anchoring within the target cancer cell. This multi-stage targeting approach effectively inhibited the critical OXPHOS energy pathway specifically within glioblastoma cells in their model.

Beyond cancer cell membranes, membranes derived from other cell types have also been extensively explored for constructing brain tumor-targeting NCs. Membranes derived from immune cells, such as macrophages [112], dendritic cells (DCs) [234], natural killer (NK) cells [115, 235], and neutrophils [167, 236–238], can potentially achieve targeting by leveraging their inherent abilities for specific tumor cell recognition or chemotactic migration towards tumor-associated inflammatory signals.

Promoting targeted neural repair and regeneration remains a significant challenge. NPs coated with membranes from neural cells offer a promising strategy. Research have indicated that NPs enveloped by membranes from various CNS cell types can exhibit high selectivity for specific recipient cell types. For example, recent work demonstrated that poly(ε-caprolactone) NPs (PCL-NPs) coated with microglial membranes (DPP-PCL-M Mem) exhibited preferential uptake by oligodendrocytes (OLs) while simultaneously reducing microglial activation [239]. Adding to this, another study found that neural cell membrane-coated DNA nanogels (NCM-nanogels), incorporating membranes from astrocytes, microglia, cortical neurons, or oligodendrocyte progenitor cells (OPCs), showed improved cellular uptake by astrocytes, microglia, cortical neurons, and oligodendrocytes compared to uncoated nanogels [240]. Indeed, these studies highlighted the versatility of membrane coatings for tuning targeting specificity, with the latter study even observing selective uptake of OPC membrane-coated DNA nanogels (NCM-O mem) by oligodendrocytes *in vitro* and *in vivo*. In addition to strategies using differentiated neural cell membranes, neural stem cell (NSC) membrane-coated NPs were reported to exhibit a high degree of targeting specificity towards neurons, a property attributed to the inherent brain-homing and neuron-recruiting capabilities of NSCs [241, 242]. This preferential targeting facilitates the delivery of therapeutic agents directly to neurons, potentially promoting repair and regeneration, making this approach particularly relevant for treating neurodegenerative diseases.

For treating ischemic stroke, platelet membrane-coated NPs represent a prominent strategy, owing to the natural tendency of platelets to accumulate at sites of vascular injury and inflammation. Rich in adhesion molecules like P-selectin and GPIIb/IIIa, platelet membranes facilitate targeted delivery by specifically binding to corresponding ligands upregulated on damaged endothelial cells and other activated platelets, leading to effective accumulation of therapeutic payloads [243–245]. Complementing this, monocyte membrane-coated NPs offer another strategy for targeting damaged vascular endothelium in stroke [246]. Monocyte membranes express integrin α4β1, which specifically binds to vascular cell adhesion molecule-1 (VCAM-1), a protein highly expressed on inflamed endothelial cells post-stroke. This interaction reportedly not only promotes NP targeting but also competitively blocks the adhesion of endogenous monocytes, potentially reducing inflammatory cell infiltration and mitigating the inflammatory cascade.

5.4 Stimuli-mediated targeting

A diverse array of stimuli, encompassing both endogenous cues inherent to the pathological microenvironment (e.g., redox state, ROS levels) and externally applied physical triggers (e.g., FUS,

light), can be strategically exploited not just for lesion accumulation but also for enhancing cell specificity within the lesion. These stimuli can act as activators or modulators, guiding engineered delivery systems to preferentially interact with, be internalized by, or release their payload within desired cellular targets amidst the complex milieu of the brain lesion. The following examples illustrate how various stimuli-responsive strategies can promote this crucial cell-specific targeting within diseased brain regions.

Brain diseases often lead to intracellular redox imbalances within the lesion. Notably, tumor cells typically exhibit a strongly reducing intracellular environment due to elevated glutathione (GSH) levels, while damaged neurons may display redox alterations linked to oxidative stress. Redox-responsive NCs exploit this intracellular distinction: they incorporate redox-sensitive linkages (e.g., disulfide bonds) that remain stable extracellularly. However, following internalization by specific target pathological cells, these bonds are cleaved within the unique intracellular reducing conditions. This mechanism, triggered by the target cell's internal environment, acts as a precise switch, releasing the payload directly within that cell population. This inherently enhances the cell-targeting specificity. For example, in brain tumor models, after NCs were endocytosed by tumor cells, the high intracellular GSH environment triggered drug release, enabling precise killing of cancer cells [247–249]. This was further enhanced by combining redox-sensitivity with surface ligands (e.g., transferrin, iRGD peptides) that first promoted efficient uptake by specific tumor or associated cells before the internal environment triggered release [247, 250]. In therapeutic strategies explored for neurodegenerative diseases like AD, this intracellular response was employed with even greater sophistication: NCs were first taken up by neurons; the intracellular reducing environment then cleaved a disulfide bond, releasing a mitochondrial targeting peptide (MPP). This MPP subsequently guided the payload (e.g., curcumin) to mitochondria within that same neuron, achieving precise subcellular localization [251]. Therefore, leveraging intracellular redox differences represents a powerful strategy for achieving highly specific targeted therapy.

High ROS levels, characteristic of brain lesions, can be exploited not only for broad lesion targeting but also to enable specific cell engagement within that area. For instance, ROS-triggered size reduction and morphological changes in NBP nanodrugs reportedly enhanced both BBB penetration and, potentially via exposed ligands like SHp, promoted binding to specific cells such as neurons and endothelial cells [252]. Similarly, a copper-based nanoplatform utilized ROS-sensitive linkers that cleaved in high-ROS environments to release copper ions [253]. These ions reportedly exerted dual effects: scavenging ROS to modulate the lesion microenvironment and directly protecting neurons. These examples demonstrate how ROS-responsive strategies can bridge macroscopic lesion localization with microscopic, cell-specific engagement.

External physical stimuli, such as FUS, can deliver energy precisely to the lesion and also be strategically used to activate specific responses within or on particular cells, enabling fine-tuned cellular intervention. For example, hybrid lipid-polymer PNPs exemplified this: under FUS stimulation, their piezoelectric core generated a local electric field [170]. This electrical stimulation reportedly acted directly on glioblastoma cells, activating their intracellular calcium channels to specifically inhibit cancer cell migration/invasion and promote apoptosis/necrosis. Similarly, MoS_2 nanosheets reportedly deformed under FUS exposure, causing a local surface charge rearrangement [171]. This effect not only enhanced chemotherapy uptake by tumor cells but crucially, selectively activated voltage-gated calcium channels on the tumor cell membrane. This targeted activation triggered calcium overload, leading to apoptosis of these specific tumor cells via a unique "sono-electro-chemical" cascade.

Following a similar principle, light, particularly NIR light, can synergize with nanotechnology for precise cell-level interventions. For example, in Parkinson's disease research, a nanosystem (ATB NPs), delivered via injection and functionalized with antibodies, specifically bound to dopamine neurons expressing target receptors (TRPV1) within the substantia nigra [254]. Critically, external NIR light then acted as the trigger. It was selectively absorbed by the nanosystem already bound to the target neurons, converting into localized heat. This heat subsequently acted directly upon these specific, engaged neurons, reportedly both activating their TRPV1 channels for neuromodulation and triggering therapeutic peptide release from the nanosystem to clear pathological proteins within those same cells. Thus, the external light activated the nanosystem precisely where it was bound to the target cells, leading to highly specific treatment.

5.5 Lysosome escape

Achieving effective cell-specific targeting requires more than merely delivering NCs to the target cell surface or even into the cell via endocytosis. Once internalized, NCs often become sequestered within the endo-lysosomal pathway, facing a harsh environment containing degradative enzymes and acidic pH that can rapidly destroy the therapeutic payload before it reaches its intended intracellular site of action (e.g., cytoplasm, nucleus, mitochondria). Therefore, facilitating efficient lysosomal escape, the release of the NC or its cargo from these compartments into the cytosol, represents a critical, often final, hurdle. Overcoming this barrier is essential for the overall success of many intracellular targeting strategies, as it is the necessary step enabling the payload to exert its therapeutic function within the designated cell type.

To address this "last mile" challenge of intracellular delivery within targeted cells, various innovative approaches have been developed to promote escape from the endo-lysosomal pathway. For instance, Plofsomes were described as fusogenic liposomes whose membrane-merging capability was initially blocked by an ROS-cleavable linker [255]. This "ock" reportedly broke specifically within the high-ROS tumor microenvironment, triggering fusion with the endosomal membrane and enabling cytoplasmic release of cargo like siRNA. Another approach utilized biological mimicry. Virus-Mimicking NPs (VMNs) incorporated a viral protein (JEV E protein) that reportedly underwent conformational changes in the acidic endosome, mediating fusion between the VMN and endosomal membranes, thereby releasing siRNA directly into the cytoplasm [256]. The efficiency of such processes could be further enhanced by optimizing lipid composition. A further mechanism involved environment-triggered structural disassembly. Engineered ferritin carriers like tHFn(+) were designed to disassemble within the acidic endosome [79]. This process exposed internal positive charges, which then were proposed to promote siRNA release from the endosome, potentially through charge interactions or the 'proton sponge' effect. These distinct methods, including environment-triggered fusion, biomimetic fusion, and controlled disassembly, aim to effectively overcome the endo-lysosomal barrier, enabling functional intracellular drug delivery subsequent to successful cell targeting.

6 Alternative delivery routes bypassing the blood-brain barrier

While systemic intravenous administration remains a prevalent approach for drug delivery, achieving therapeutic concentrations within the brain is often severely hampered by the restrictive nature of BBB. To circumvent this critical obstacle and enhance drug delivery to CNS, several alternative administration routes have been investigated, aiming to bypass or modulate the BBB more directly.

6.1 Nose-to brain delivery

Nose-to-brain drug delivery offers a non-invasive pathway for administering therapeutics directly to the CNS via the nasal cavity, effectively bypassing the BBB. This delivery mechanism primarily relies on transport along neuronal pathways, including the olfactory and trigeminal nerves, as well as associated vascular routes [257]. The key potential benefits of this approach are significant: it circumvents the BBB and avoids hepatic first-pass metabolism, which was reported to enhance drug bioavailability [258, 259] and potentially facilitate a rapid onset of action [260]. Additionally, the method is non-invasive and user-friendly, often resulting in fewer systemic side effects compared to systemic administration [258, 259].

However, this route faces inherent challenges. Physiological limitations include a restricted absorption window due to rapid mucociliary clearance mechanisms, constraints on the administrable volume per dose, and potential enzymatic degradation within the nasal cavity [261]. Furthermore, the use of NP systems introduces specific considerations, such as potential neurotoxicity, the risk of unintended pulmonary deposition via inhalation, formulation variability impacting consistent performance, challenges and costs associated with manufacturing scale-up, and potential loss of the delivery system during uptake processes [262, 263].

Despite these hurdles, nose-to-brain delivery remains a promising strategy for targeting the brain[264–267], particularly for applications requiring rapid drug administration, such as intervening in epileptic seizures. It also holds potential for improving CNS access for drugs that are otherwise difficult to deliver effectively due to low systemic bioavailability, extensive metabolism, or poor BBB permeability [258].

6.2 Intrathecal (IT) injection

IT injection involves the direct administration of therapeutics into the cerebrospinal fluid (CSF) within the subarachnoid space, thereby completely bypassing the BBB for efficient CNS targeting [9]. Once introduced into the CSF, nanocarrier (NC) systems can interact with CSF components and distribute throughout the CNS via CSF bulk flow and diffusion [268].

Combining nanotechnology with IT administration offers several potential advantages. These include enhancing the solubility and stability of poorly soluble drugs, potentially prolonging residence time within the CSF compared to free drugs, and enabling controlled drug release to reduce dosing frequency [234, 269]. Similar to strategies employed for systemic delivery, surface modification of IT-administered NCs could enhance targeting capabilities towards specific cells or regions within the CNS accessible from the CSF [270].

However, this approach presents significant challenges. Beyond the inherent invasiveness of the lumbar puncture procedure required for IT injection and associated risks (e.g., infection, headache, CSF leakage), accurately predicting and controlling NP behavior within the complex CSF environment remains particularly difficult. Factors such as aggregation, clearance pathways (e.g., via arachnoid villi, glymphatic system, or nerve root egress), and complex distribution patterns pose non-trivial hurdles [9]. Consequently, clinical implementation necessitates a careful evaluation of potential therapeutic benefits against these inherent risks.

6.3 Intracerebral (IC) injection

IC injection represents a highly direct drug delivery method where nanoformulations are administered directly into specific brain regions. This technique typically involves creating a small burr hole in the skull surgically and utilizing stereotactic guidance to inject the NC system precisely into the target parenchymal site. This method has been used experimentally to deliver various NCs, such as lipid NPs carrying mRNA for localized gene expression [10] or specialized NPs designed to enhance local tumor treatment efficacy [271, 272].

IC injection completely bypasses the BBB and avoids systemic clearance, potentially achieving very high local drug concentrations and rapid onset of action at the target site [10, 271, 273]. However, the procedure is highly invasive, carrying inherent surgical risks (e.g., bleeding, infection, damage to surrounding tissue). Furthermore, achieving uniform drug distribution over a large volume is challenging, with diffusion often restricted primarily to the area immediately surrounding the injection site, representing another significant limitation [10].

6.4 Convection-enhanced delivery (CED)

CED is another direct brain delivery strategy designed to overcome the limitations of simple diffusion following IC injection. CED utilizes a maintained pressure gradient via a specialized infusion catheter to induce bulk fluid flow (convection) through the brain's interstitial space, achieving wider and more homogenous drug distribution over larger volumes compared to passive diffusion alone [274]. The properties of the infused NCs play a critical role in CED performance. For instance, a study using real-time PET monitoring during CED in minipigs investigated the impact of particle size; it found that larger NPs (130 nm liposomes) resulted in a superior distribution volume and longer retention within the brain compared to smaller gold NPs (8 or 40 nm) under their experimental conditions [275].

Combining NCs with CED offers synergistic advantages for brain-targeted delivery. Key benefits arise from the NCs themselves, which can protect drugs from degradation, enhance stability, enable sustained release profiles, and prolong retention time within the target tissue [276]. Additionally, surface modifications on the NCs can potentially allow for more precise targeting of specific cells or pathological features within the infused region while minimizing uptake or effects on healthy tissue [277].

Despite its promise for bypassing the BBB and improving distribution, CED faces significant practical hurdles. Technically, optimizing catheter design and placement accuracy, along with developing reliable methods for real-time monitoring of infusate distribution, remain key challenges [278]. Clinically, managing potential treatment-related complications, such as catheter reflux, leakage into unintended spaces, or procedure-induced cerebral edema, presents major difficulties, underscoring the complexity of

successfully implementing this technique.

6.5 Cervical subcutaneous injection

Meningeal lymphatic vessels (mLVs), located within the dura mater surrounding the brain, provide a crucial interface between the CNS and the peripheral immune system, playing roles in CSF drainage and immune surveillance [279]. While they primarily facilitate anterograde drainage of CSF components and brain metabolites towards the deep cervical lymph nodes (dCLNs), their unique anatomical structure, lacking valves and smooth muscle, also potentially permits retrograde transport under certain conditions. Research confirmed that NPs injected directly into these cervical lymph nodes could travel retrogradely along the lymphatic network into the meninges and potentially access the brain parenchyma, thus bypassing the BBB and presenting a novel route for brain drug delivery [280].

This concept of retrograde lymphatic access has inspired the exploration of less invasive approaches. For instance, Dai *et al.* explored subcutaneous neck injections targeting dCLNs for treating breast cancer brain metastases using multifunctional nanoprobes [281]. One probe (α-PLNP) facilitated dual-modal lymphatic imaging, while the other (α-M-PLNP), loaded with melittin and targeting SR-B1, reportedly stimulated local anti-tumor T cell responses within the lymph nodes. This strategy aimed to achieve a precision theranostic immunotherapy outcome by modulating the immune response relevant to brain metastases via this lymphatic route. Further research is needed to fully understand the efficiency and applicability of targeting the brain via subcutaneous administration aimed at retrograde meningeal lymphatic transport (Fig. 8).

7 Clinical translation of brain-targetic nanomedicines

The extensive preclinical research discussed in this review has yielded a multitude of innovative strategies for treating CNS disorders. To provide a consolidated overview of these advancements, Table 2 summarizes representative nanoparticle-based therapeutic approaches for various conditions, including glioblastoma, ischemic stroke, and Alzheimer's disease. This table highlights the diversity of nanoparticle systems, their underlying targeting mechanisms, and their reported outcomes.

Despite the breadth of preclinical success, the translation of these technologies into clinical practice remains a formidable challenge. A select few nanomedicines have, however, progressed to clinical trials, demonstrating the tangible potential of this field. Key examples, which are detailed in Table 2, include 2B3-101 [282], a liposomal system designed to enhance BBB penetration, and AGuIX®, a nanoparticle developed as a radiosensitizer for brain tumor therapy [283]. The progression of these candidates is crucial for validating the promise of brain-targeting nanomedicine, yet the small number also underscores the significant hurdles that must be overcome to achieve widespread clinical impact.

One study (NANORAD2, NCT03818386) is assessing its combination with whole-brain radiation therapy (WBRT) for the treatment of brain metastases. This followed a Phase 1b trial (NCT02820454) which had confirmed its manageable safety profile in this setting [283, 284].

A second trial (NANO-GBM, NCT04881032) is evaluating its efficacy when added to standard chemoradiation for newly diagnosed glioblastoma. Prior Phase I/II results (NCT02820454, extended cohort) had indicated good safety and suggested potential

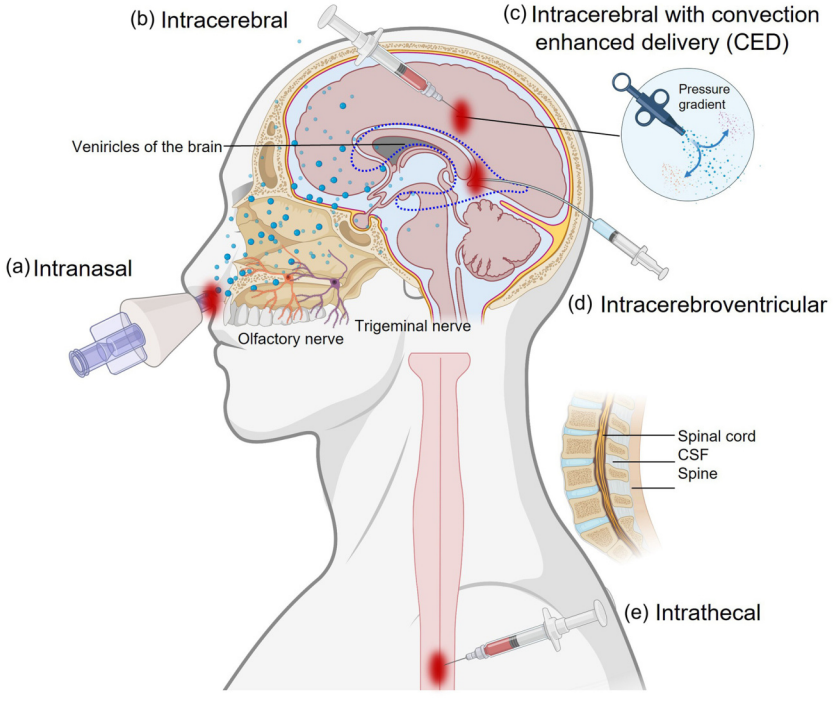

Figure 8 Non-systemic delivery routes to the central nervous system. Alternative administration routes bypassing BBB to deliver therapeutic agents, including nanocarriers, directly to CNS. These approaches are relevant when systemic administration is inefficient due to BBB impermeability. (a) Intranasal delivery: Agents administered into the nasal cavity traverse olfactory and trigeminal nerves to reach the brain parenchyma. (b) Intracerebroventricular injection: Direct administration into the brain's ventricular system allows subsequent diffusion into surrounding brain tissue. (c) Convection-enhanced delivery (CED): Agents infused directly into the brain parenchyma using a pressure gradient (inset illustration) achieve widespread distribution within a localized brain region. (e) Intrathecal injection: Administration into CSF space surrounding the spinal cord facilitates distribution within the CSF throughout the brain and spinal cord.

Table 2 Representative nanoparticle-based therapeutic strategies for CNS disorders

CNS disorder	Nanoparticle system & payload	Targeting strategy	Key outcome/status	Ref.
Glioblastoma	pH-responsive liposome (Doxorubicin)	pH-sensitive peptide for tumor recognition & drug release in acidic microenvironment.	Enhanced tumor-specific delivery and therapeutic efficacy.	[138]
	MMP-2 responsive NC (Bispecific Ab, dEGCG)	Enzyme-triggered release of payload in MMP-2 rich tumor microenvironment.	Synergistic ferroptosis and T-cell-mediated immune response.	[150]
	Cancer cell membrane-coated NP (Gboxin)	Homotypic targeting via cancer cell membrane; mitochondrial targeting via hybrid membrane.	Precise mitochondrial drug delivery, inhibiting tumor energy metabolism.	[234]
Ischemic stroke	ROS-responsive CeNP (Edaravone)	Intrinsic ROS scavenging (CeO_2 core) and "protection-during-transcytosis".	Minimized BBB injury during transit and enhanced neuroprotection.	[155]
	Neutrophil membrane-coated NP	Chemotaxis-driven homing to inflammatory signals at the lesion.	Targeted delivery to the ischemic region, mimicking natural immune cell migration.	[165]
Alzheimer's disease	ROS-responsive nanovesicles (siRNA, BDNF mRNA)	ROS-sensitive linker for co-release of dual genetic payloads in high-ROS environment.	Site-specific gene therapy to reduce Aβ production and promote neuronal survival.	[157]
Parkinson's disease	RVG-peptide modified NP	RVG peptide targets a receptor on neurons for specific uptake.	Targeted delivery of therapeutics to dopaminergic neurons *in vivo*.	[204, 205]
Epilepsy	PPY/PDA-based nanocarrier (Phenytoin)	Real-time electrical sensing of seizure activity to trigger on-demand drug release.	Rapid, self-regulated drug release in response to pathological brain signals.	[164]
Brain metastases/ glioma (clinical)	2B3-101 (Glutathione-liposome with Doxorubicin)	Targets γ-glutamyl transpeptidase on BBB for enhanced penetration.	Clinical stage: completed phase I/IIa, showed favorable safety and antitumor activity.	[282]
Brain metastases/ glioblastoma	AGuIX® (Gadolinium-based NP)	Passive accumulation (EPR effect); functions as a dual MRI agent and radiosensitizer.	Clinical stage: multiple phase 2 trials assessing efficacy with radiotherapy (e.g., NCT03818386).	[283–287]

survival benefits when AGuIX® was combined with standard therapy [285, 286].

A third study (NANOBRAINMETS, NCT04899908) is exploring whether AGuIX® can improve the efficacy of stereotactic radiosurgery for refractory brain metastases, having received FDA Fast Track designation for this application in May 2024.

8 Outlook and future perspectives

Significant strides have been made in developing NP drug delivery systems for CNS applications, demonstrating immense preclinical potential for disease diagnosis and treatment. NC platforms have been successfully engineered, highlighting the vast therapeutic opportunities that nanomedicine presents in this challenging field. However, translating this preclinical promise into widespread clinical application necessitates overcoming persistent challenges related to delivery precision, efficiency, safety, and, critically, clinical translatability. Consequently, future research must concentrate on several key areas to engineer smarter, safer, and more clinically viable functional delivery platforms.

Given the significant heterogeneity of CNS pathological states, not only between patients but also within individual lesions and affected cell populations, future research must prioritize the rational design and engineering of intelligent, multi-stimuli responsive nanocarriers. Such sophisticated functional materials, capable of precisely orchestrated drug release triggered by specific combinations of microenvironmental cues, are essential for achieving enhanced therapeutic control, specificity, and minimizing off-target effects [287].

The efficient realization and refinement of these complex functional material systems necessitate the adoption of advanced rational design methodologies and high-throughput screening approaches. These efforts should integrate computational tools, such as optimization algorithms for data-driven material design and target identification [288], with experimental techniques like in vivo phage display, which has proven effective for discovering novel, high-affinity brain-targeting ligands crucial for nanocarrier functionalization and optimization [289–292]. Rigorous preclinical evaluation of emerging nanoparticle platforms remains hindered by the limitations of current in vitro model systems, which often lack sufficient physiological relevance to the complex CNS microenvironment. Continued innovation is required to develop more predictive platforms, potentially by combining advanced microfluidic technologies with organoid or "brain-on-a-chip" systems for initial material screening and optimization [293]. Crucially, promising in vitro results must be validated through systematic and comprehensive in vivo characterization protocols. These protocols should meticulously track nanocarrier biodistribution, metabolism, cellular uptake pathways, and intracellular trafficking to fully elucidate their complex behavior within a living system. Understanding the distribution and effects of nanoparticles and their payloads across diverse brain cell types, and their impact on cross-cell communication, requires particular emphasis, especially within the context of the specific disease microenvironment, as suggested by prior studies investigating NP interactions in complex biological settings [294–297]. Ultimately, facilitating the crucial step of clinical translation necessitates the establishment of standardized production and evaluation frameworks. This imperative requires simplifying nanocarrier system designs while retaining core functionalities, developing robust, unified manufacturing processes and quality control standards amenable to scalable production, and formulating standardized, widely accepted preclinical and clinical evaluation protocols to consistently assess material performance, safety, and efficacy across diverse platforms and research groups.

In summary, realizing the full therapeutic potential of brain-targeted nanoparticle delivery will increasingly rely on synergistic, interdisciplinary collaboration. Integrating advanced materials science principles with sophisticated bioengineering strategies, cutting-edge imaging technologies, and novel biological insights is essential to engineer next-generation platforms with enhanced intelligence, precision, and safety. This integrated approach holds

the potential to drive transformative breakthroughs in CNS disease therapy while addressing the critical pragmatic requirements of scalable manufacturing and successful clinical translation (Fig. 9).

Data availability

Not applicable.

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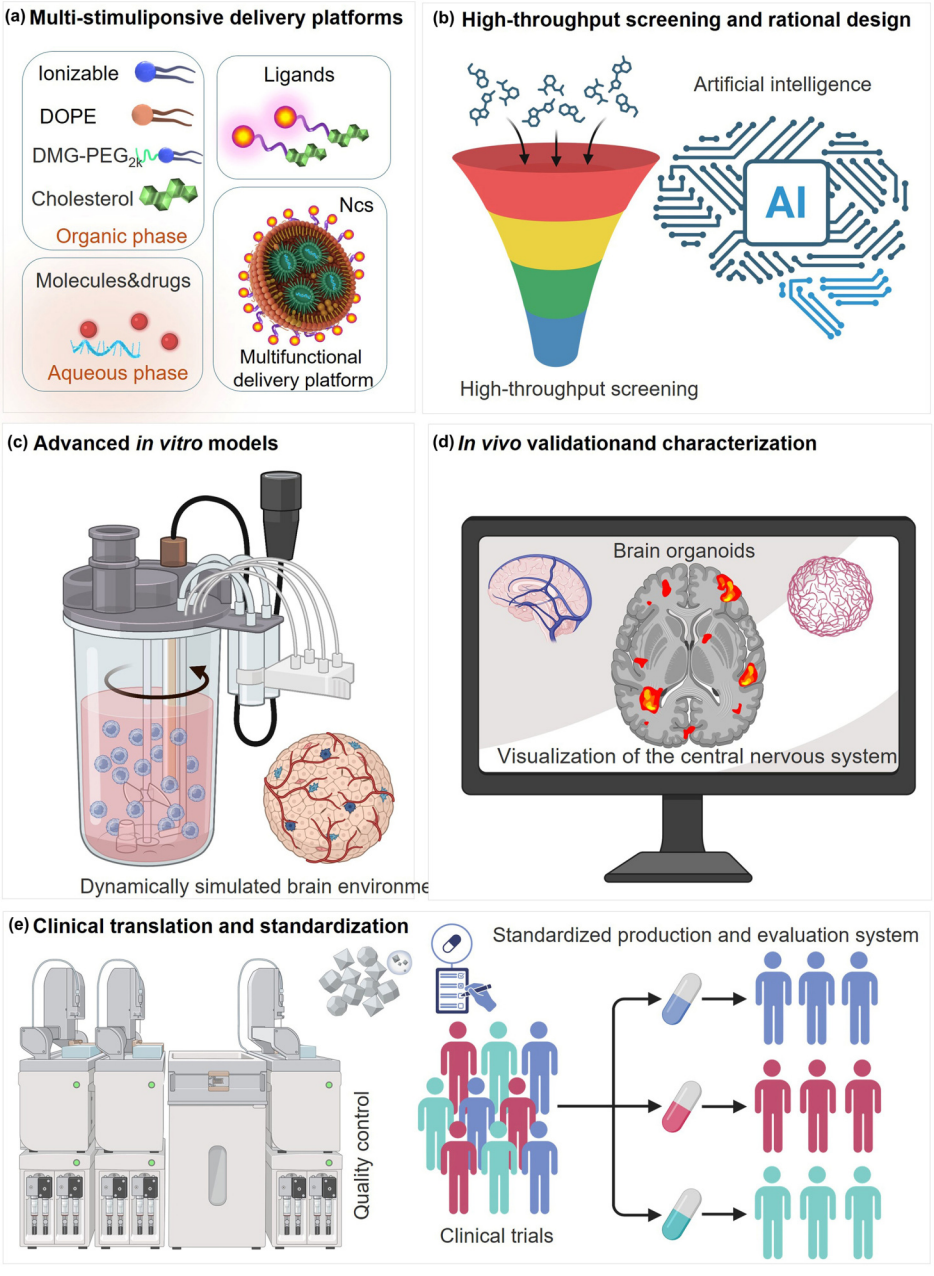

Figure 9 Advanced strategies and translational pipeline for developing central nervous system-targeted nanoparticle therapies. Key advancements and steps involved in the future development and clinical translation of intelligent nanocarrier systems for targeted drug delivery to CNS, highlighting interconnected areas crucial for progressing from design to clinical application. (a) Concept of intelligent, multi-stimuli-responsive delivery platforms, showing how various components (ionizable lipids, DOPE, DMG-PEG, cholesterol, functional molecules/drugs, targeting ligands) can be assembled to create sophisticated NCs responsive to specific biological cues. (b) Importance of high-throughput screening and rational design approaches, including the integration of artificial intelligence (AI) and big data analysis, to accelerate the identification and optimization of promising nanocarrier formulations. (c) Use of advanced *in vitro* models, such as dynamically simulated brain environment systems utilizing bioreactors and complex cell co-cultures, to better predict nanocarrier behavior and efficacy before proceeding to *in vivo* studies. (d) Critical stage of in vivo validation and characterization, demonstrating the use of non-invasive visualization techniques to track nanocarrier distribution and assess their targeting capabilities within the CNS of living organisms. (e) Necessary steps for clinical translation and standardization, including the establishment of robust, standardized production and quality control processes for scalable manufacturing, leading towards rigorous clinical trials in human patients to evaluate safety and therapeutic efficacy.

Declaration of competing interest

The authors declare no conflict of interest.

Author contribution statement

R. Y., S. G. Q., Z. H. Z., S. B. L., and J. Y. W.: Conceptualization. R. Y., Y. P. Z., X. Y. J., W. X., Y. C., L. N., and Q. S. G.: Investigation. R. Y.: Writing – original draft. R. Y., Y. P. Z., X. Y. J., W. X., Y. C., L. N., Q. S. G., J. Y. W., S. B. L., Z. H. Z., and S. G. Q.: Writing – review & editing. S. G. Q., Z. H. Z., S. B. L., and J. Y. W.: Supervision. S. G. Q., Z. H. Z., S. B. L., and J. Y. W.: Project administration.

Informed consent

Not applicable.

Ethics statement

Not applicable.

Use of AI statement

During the preparation of this work, we utilized a large language model (Google Ai studio-Gemini 2.5) for improving language, enhancing readability, refining academic tone, and ensuring scientific precision in the manuscript text and the accompanying response to reviewers. After using this AI-assisted technology, we thoroughly reviewed and edited all generated content as needed and take full responsibility for the content of the publication.

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