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Review

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Nanomedicine-enabled strategies for navigating the blood–brain barrier in Parkinson disease

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Abstract

Parkinson disease (PD) is still mainly treated with symptomatic therapies, while effective disease-modifying interventions remain limited. Although emerging therapeutics such as biologics, nucleic acid drugs, neurotrophic factors, and gene-based approaches offer new opportunities, their clinical translation is often restricted by inadequate brain delivery. Nanomedicine has, therefore, attracted increasing interest because it can improve drug stability, protect fragile cargos, enable controlled release, and support multifunctional therapeutic design. Nevertheless, the blood–brain barrier (BBB) remains the principal obstacle to effective brain-targeted therapy in PD. This review discusses nanomedicine-based delivery strategies for PD from the perspective of BBB navigation and classifies them into 2 major categories: strategies that cross the BBB and strategies that bypass it. BBB-crossing approaches include carrier-mediated transport, receptor-mediated transport, adsorptive and biomimetic transcytosis, and physically assisted methods such as focused ultrasound and photothermal modulation. BBB-bypassing approaches include intranasal delivery, meningeal lymphatic-associated pathways, skull–meninges-related microchannel routes, and local intracranial administration such as convection-enhanced delivery. We summarize their mechanisms, representative applications, advantages, and limitations, and compare them in terms of cargo suitability, delivery precision, repeatability, safety, and translational feasibility. Overall, nanomedicine provides important opportunities to expand the therapeutic potential of both conventional drugs and emerging biologics for PD. Future progress will depend on developing cargo-matched and clinically realistic delivery systems that balance brain access, therapeutic efficacy, safety, and manufacturability.

Keywords: Blood–brain barrier, Brain delivery, Drug delivery strategies, Nanomedicine, Parkinson disease

1. Introduction

Parkinson disease (PD) is the second most common neurodegenerative disorder worldwide, clinically characterized by progressive loss of dopaminergic neurons in the substantia nigra pars compacta, striatal dopamine depletion, and a broad spectrum of motor and nonmotor symptoms. Current pharmacotherapies offer symptomatic relief but remain largely palliative; long-term use is frequently constrained by diminishing efficacy, motor fluctuations, dyskinesia, and nonmotor side effects, without halting or reversing the underlying neurodegenerative process[1,2]. This therapeutic shortfall is exacerbated by the rapidly escalating global burden of the disease. PD is the fastest-growing neurological disorder in terms of prevalence and disability; the World Health Organization projects that neurodegenerative diseases, including PD and Alzheimer disease, will become the second leading cause of death globally by 2040, surpassing cancer-related mortality. The total number of PD patients worldwide is expected to reach approximately 25.2 million by 2050, imposing immense socioeconomic costs on healthcare systems and caregivers[3]. These converging factors collectively underscore the urgent and critical need for disease-modifying therapies that can effectively and safely deliver therapeutic agents to the brain.

As the understanding of PD pathogenesis has expanded from dopaminergic deficiency to include α-synuclein aggregation, oxidative stress, mitochondrial dysfunction, neuroinflammation, lysosomal impairment, and disordered neuroimmune interactions (Figure 1), the therapeutic landscape has also broadened from traditional small-molecule replacement strategies to biologics, nucleic acid therapeutics, neurotrophic factors, and gene- or cell-based interventions[4–8]. However, the development of more effective therapies for PD is constrained not only by the complexity of the disease itself but also by the difficulty of delivering therapeutically meaningful amounts of drugs to the brain[9]. Many promising agents show strong neuroprotective or disease-modifying potential in principle, yet fail to achieve sufficient intracerebral exposure after systemic administration[10]. This limitation is especially pronounced for proteins, antibodies, nucleic acids, and other macromolecular therapeutics, whose pharmacological promise is often offset by poor stability, rapid peripheral clearance, and restricted access to the central nervous system (CNS)[11]. Therefore, in PD, the key challenge is often not simply whether a therapeutic molecule can be identified, but whether it can be delivered efficiently, safely, and reproducibly to disease-relevant brain regions[12].

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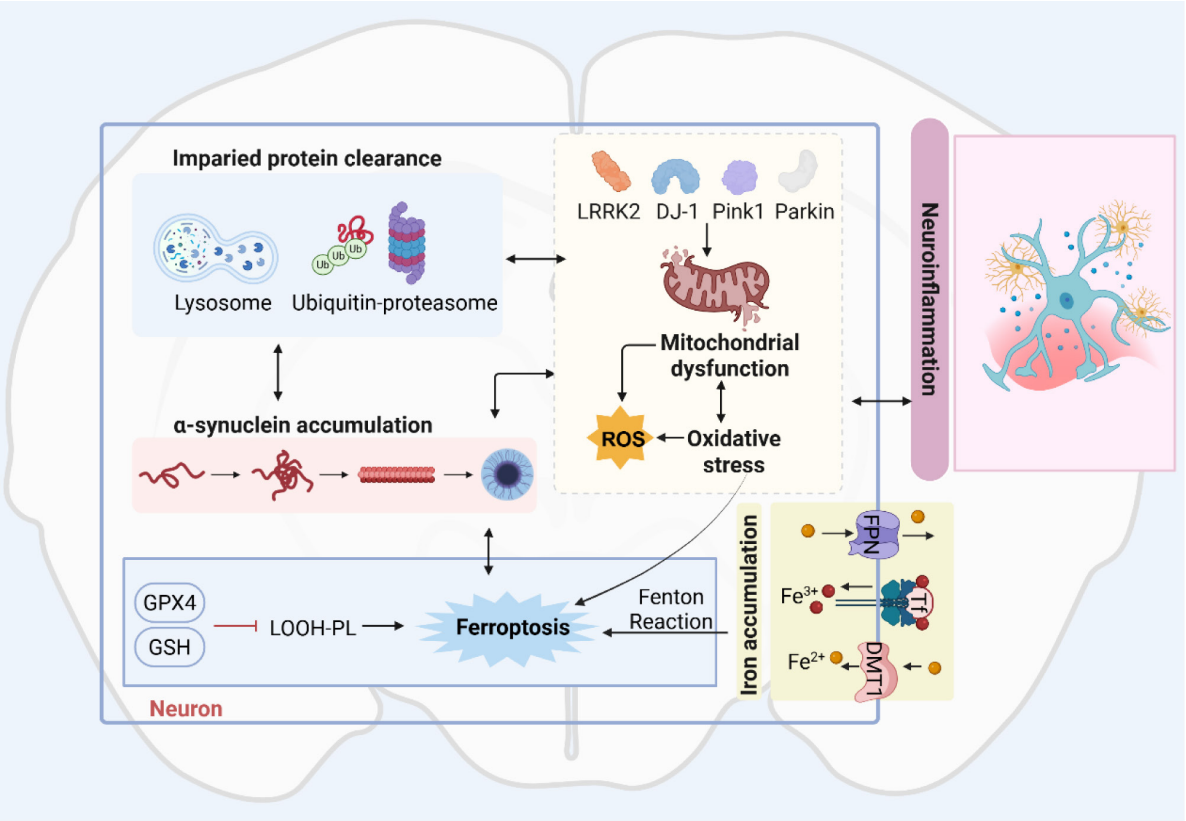


Figure 1. Major pathogenic mechanisms involved in Parkinson disease. This schematic illustrates the interconnected pathogenic processes underlying Parkinson disease. Impaired protein clearance, mitochondrial dysfunction, oxidative stress, iron accumulation, ferroptosis, and neuroinflammation interact to promote α-synuclein accumulation and dopaminergic neuronal injury. PD-related genes, including LRRK2, DJ-1, PINK1, and Parkin, contribute to mitochondrial and proteostatic dysfunction, further aggravating cellular stress.

In this context, nanomedicine has emerged as a highly attractive platform for PD therapy. By enabling drug protection, controlled release, multifunctional integration, and flexible surface engineering, nanoplatforms offer opportunities to improve the therapeutic performance of both conventional drugs and emerging biologics without necessarily redesigning the active molecule itself[13]. At the same time, nanomedicine does not automatically solve the brain delivery problem. The blood–brain barrier (BBB), as a highly selective neurovascular interface, continues to represent the central biological obstacle to effective CNS therapy. Even when nanocarriers improve drug stability or circulation, they still face the fundamental challenge of crossing or circumventing this barrier in a manner that is efficient, regionally relevant, and clinically feasible[14].

Accordingly, current nanomedicine-based approaches for PD can be understood from a delivery perspective as 2 broad and complementary categories: strategies designed to cross the BBB and strategies intended to bypass it[15,16]. The former include carrier-mediated, receptor-mediated, adsorptive, biomimetic, and physically assisted approaches that attempt to negotiate directly with the barrier[17]. The latter seek alternative routes to the brain, such as intranasal delivery, meningeal-associated pathways, skull–meninges-related channels, or local intracranial administration[18–20]. Each category offers distinct opportunities, but each is also shaped by different constraints in transport efficiency, regional distribution, repeatability, safety, and translational practicality.

In this review, we first summarize the current pharmacotherapy of PD and its limitations, and then discuss why nanomedicine provides a meaningful therapeutic and delivery framework for this disease. We next examine the BBB as the central obstacle to brain delivery, followed by a systematic discussion of nanomedicine strategies for crossing or bypassing the BBB. Finally, we compare these 2 strategy groups from a translational perspective and outline the key challenges and future directions for clinically realistic nanomedicine design in PD. Through this framework, we aim to highlight that the future of PD brain delivery lies not in identifying a single universally optimal route, but in developing cargo-matched, target-aware, and clinically translatable delivery strategies.

2. Current treatment strategies for PD and their limitations

Current pharmacotherapy for PD remains predominantly symptomatic[21]. Levodopa, as the gold standard, effectively ameliorates motor symptoms. However, its long-term use is inevitably associated with motor complications such as wearing-off phenomena and dyskinesia, and its efficacy progressively declines with disease progression[22]. Dopamine agonists, monoamine oxidase-B inhibitors, and catechol-O-methyltransferase inhibitors are frequently employed as adjunctive agents to prolong dopaminergic stimulation, yet they are equally incapable of halting the neurodegenerative process[23]. Nondopaminergic drugs, such as anticholinergics and amantadine, provide only supportive symptomatic benefit[24–26]. From a drug delivery perspective, current therapies carry inherent shortcomings: even for levodopa, the cornerstone of clinical management, brain uptake is highly variable due to extensive peripheral metabolism and competition with large neutral amino acids, making precise control of central exposure difficult to achieve[22].

For patients with advanced or medically refractory disease, deep brain stimulation can markedly improve symptoms by modulating pathological activity in the basal ganglia circuits[27].

Nevertheless, the procedure is invasive, resource-intensive, and associated with surgical risks, hardware-related complications, and neuropsychiatric adverse effects[28]. With respect to regenerative and restorative strategies, cell replacement therapies using fetal tissue, induced pluripotent stem cells, or embryonic stem cell-derived dopaminergic neurons have raised considerable hope[29], but limited graft survival, insufficient functional integration, immunological concerns, and safety issues have prevented their translation into widely applicable clinical solutions. Taken together, neither existing pharmacological nor surgical interventions can arrest disease progression[30].

With increasing insight into the molecular pathogenesis of PD, disease-modifying therapies have become a central research priority. Representative strategies include reducing the α-synuclein burden, interfering with its aberrant aggregation and cell-to-cell propagation, and suppressing the expression of disease-causing genes using antisense oligonucleotides or small interfering RNAs[31,32]. However, the most promising disease-modifying candidates, such as anti-α-synuclein antibodies, RNA-based therapeutics, and neurotrophic factors, are biologics or nucleic acid-based agents. Following systemic administration in their free form, these molecules confront a 3-fold delivery barrier: negligible penetration across the BBB, rapid enzymatic degradation in plasma, and the consequent failure to reach therapeutically effective concentrations within the brain parenchyma[33]. In essence, the core challenge is not the lack of pharmacologically active molecules, but the inability of these molecules to access their intracranial targets in sufficient quantities.

This delivery predicament is not unique to disease-modifying approaches; existing small-molecule drugs such as levodopa likewise suffer from highly variable brain uptake and poorly controllable BBB penetration. The key delivery bottleneck facing pharmacotherapy for PD can therefore be formulated as follows: how to deliver centrally active therapeutic molecules, whether small molecules or biologics, across the BBB at sufficient concentrations and with spatiotemporal control to reach the diseased regions[34]. Nanomedicine offers a systematic engineering framework to overcome this bottleneck. In contrast to conventional formulations, nanocarriers can simultaneously fulfill multiple functions: protecting fragile payloads from enzymatic degradation, prolonging systemic circulation half-life, actively traversing the BBB via mechanisms such as receptor-mediated transcytosis and adsorptive-mediated transcytosis (AMT), or bypassing the barrier through routes such as intranasal delivery and the meningeal lymphatic pathway. It is precisely this versatile and engineerable nature that positions nanomedicine as one of the most promising platforms for solving the brain delivery challenge in PD.

3. Nanomedicine provides distinct therapeutic and delivery advantages for PD

The progression of PD is driven collectively by α-synuclein aggregation, oxidative stress, mitochondrial dysfunction, ferroptosis, neuroinflammation, and other factors[35]. However, conventional drugs are largely ineffective at blocking these pathological processes due to low BBB penetration efficiency, short half-life, poor targeting, and significant systemic toxic side effects. The limitations of current pharmacotherapy have prompted increasing interest in therapeutic platforms that can improve drug performance without necessarily redesigning the active pharmaceutical ingredient itself. In this context, nanomedicine has emerged as a promising strategy for PD[14].

One important advantage of nanomedicine lies in its ability to improve the delivery profile of existing small-molecule drugs. Many conventional agents suffer from suboptimal aqueous solubility, rapid clearance, poor metabolic stability, or unfavorable systemic distribution[36]. Nanocarriers can mitigate some of these limitations by enhancing drug solubilization, prolonging circulation time, modulating biodistribution, and reducing premature degradation[37]. Such formulation-level optimization is particularly attractive in PD, where long-term treatment is often required and where maintaining more stable therapeutic exposure may help improve efficacy and tolerability. In this sense, nanomedicine does not simply replace established drugs, but may expand the therapeutic value of already available pharmacological agents[38].

Nanomedicine is also especially relevant for the delivery of biologics and other vulnerable therapeutic cargos that are difficult to use in conventional formulations. Proteins, peptides, nucleic acids, and other macromolecular therapeutics are often limited by poor stability, enzymatic degradation, rapid systemic elimination, or loss of bioactivity before reaching the desired site of action[39,40]. By providing a protective microenvironment, nanoplatforms can help preserve the integrity of these cargos and improve their in vivo persistence[41]. This feature is of particular importance for emerging PD therapies aimed at reducing α-synuclein burden, modulating pathogenic gene expression, or restoring cellular function, many of which rely on fragile biological molecules rather than traditional small drugs[42].

Beyond simple drug protection, nanomedicine offers opportunities for controlled and multifunctional therapy. Through rational design of material composition and nanostructure, nanocarriers can be tailored to achieve sustained release, stimulus responsive release, or codelivery of multiple therapeutic agents[43,44]. These properties are potentially valuable in PD, a multifactorial neurodegenerative disorder involving dopaminergic neuron loss, α-synuclein aggregation, oxidative stress, mitochondrial dysfunction, and neuroinflammation[45]. Because a single intervention may be insufficient to address such a complex pathological network, nanoplatforms provide an attractive basis for combination therapy and multimodal intervention. In addition, some nanomaterials may contribute auxiliary functions such as reactive oxygen species (ROS) scavenging, imaging contrast, or energy responsiveness, further broadening their therapeutic potential[46,47].

Another major strength of nanomedicine is its high degree of engineerability. Nanoparticles can be tuned in terms of size, shape, surface charge, material composition, ligand decoration, and biomimetic coating, creating opportunities to optimize their biological behavior in a more versatile manner than is usually possible with free drugs alone[48,49]. This structural tunability is particularly important in brain-targeted therapy, where therapeutic success depends not only on the intrinsic activity of the cargo but also on whether it can be delivered to the relevant brain regions in sufficient amounts and with acceptable safety[50,51]. Thus, the value of nanomedicine in PD lies not merely in carrying drugs, but in enabling programmable interactions between therapeutic agents and biological barriers.

Leveraging these engineering advantages, nanomedicines can transcend the limitations of conventional therapies, enabling precision design against the core pathologies of PD and advancing toward disease-modifying treatment. For instance, α-syn aggregation represents a hallmark pathological event that can be targeted through nanomaterial–protein interactions. Nanomaterials can prevent fibrillization through specific surface interactions with hydrophobic regions of α-syn; for example, carboxyl groups on the surface of quantum dots can induce the disassembly of preformed α-syn fibrils into nontoxic monomers[52,53]. Regarding the progressive loss of dopaminergic neurons in the nigrostriatal pathway, which is the pathological alteration directly responsible for clinical symptoms, nanocarriers are required to achieve specific delivery to and long-term protection of this pathway. Encapsulating levodopa in PEGylated liposomes or poly(lactic-*co*-glycolic acid) nanoparticles enables sustained intracranial drug release, significantly reducing the "on–off" phenomenon and motor complications associated with oral administration[54]. For large-molecule proteins susceptible to enzymatic degradation, such as glial cell line-derived neurotrophic factor (GDNF), nanocarriers not only provide

effective protection but can also be surface modified with ligands to achieve precise targeting of dopaminergic neurons[55].

Neuroinflammation acts as a disease amplifier throughout the entire course of PD, with its core pathological feature being the excessive activation of microglia into a pro-inflammatory M1 phenotype and the concomitant release of abundant inflammatory cytokines, which necessitates the precise targeting of activated microglia by nanocarriers. Certain nanomaterials possess intrinsic immunomodulatory activities; cerium oxide nanoparticles can simultaneously scavenge ROS and inhibit microglial activation[56]. Oxidative stress and mitochondrial dysfunction, as the final common pathways leading to neuronal death in PD, have driven the development of mitochondria-targeted antioxidant nanosystems. By modifying nanocarriers with the lipophilic cation triphenylphosphine, therapeutic agents can be accumulated in the mitochondrial matrix, driven by the mitochondrial membrane potential, thereby significantly improving mitochondrial function and reducing ROS production[57]. The characteristic microenvironment of the PD brain, including elevated ROS levels and increased matrix metalloproteinase (MMP) activity, provides natural triggers for the design of stimuli-responsive smart nanocarriers. For example, block copolymer nanoparticles containing ROS-sensitive chemical bonds such as thioether or boronate ester linkages undergo rapid drug release under the high-ROS conditions in the PD brain[58]; and nanoparticles modified with MMP-9-sensitive peptides can release drugs specifically at inflammatory sites, further enhancing therapeutic safety and efficacy[59].

Despite remarkable progress in nanomedicine design based on PD pathological features, numerous challenges remain: nanoplatforms are not inherently capable of efficient brain delivery, nor do they guarantee clinical benefit simply by virtue of nanoscale design. Their real promise lies in the possibility of rational engineering: by improving drug stability, supporting multifunctional therapy, and offering flexible interfaces for biological interaction, nanomedicine creates new opportunities to enhance PD treatment. At the same time, these opportunities can only be realized if the central obstacle to brain delivery, that is, the BBB, is effectively addressed[60]. Importantly, this barrier is not unique to nanomedicine; it represents a fundamental challenge for virtually all therapeutic agents aimed at the CNS. Thus, the key question is not whether nanomedicine faces the BBB, but how its engineerability can be leveraged to address a barrier that equally limits conventional therapies. This leads to the next question: why brain delivery remains so difficult and how the BBB continues to constrain nanomedicine-based interventions in PD.

4. The BBB as the central obstacle to brain delivery in PD

The BBB is a highly specialized and selectively permeable interface that regulates molecular exchange between the systemic circulation and the CNS. By maintaining the biochemical stability of the brain microenvironment and limiting the entry of harmful substances, the BBB plays an essential role in preserving neuronal function and CNS homeostasis[61]. However, the same properties that protect the brain also create a major obstacle for therapeutic intervention in general, regardless of whether the drug is a conventional small molecule, a biologic, or a nanoparticle-based formulation. Efficient and sustained delivery to specific brain regions remains exceptionally difficult for the vast majority of therapeutic agents[62].

Importantly, the BBB is not a single anatomical wall, but a dynamic and integrated neurovascular system. Its structural basis is formed primarily by brain microvascular endothelial cells (BMECs), which are tightly connected and supported by pericytes, astrocytic end-feet, and the basement membrane (Figure 2)[63]. Among these components, BMECs constitute the principal physical barrier by severely restricting paracellular diffusion and tightly regulating transcellular transport[64]. Pericytes contribute to vascular stability, barrier integrity, and local homeostatic regulation, while astrocytes help maintain BBB properties through close neurovascular signaling and modulation of endothelial function. Together, these cellular and extracellular elements establish a highly selective interface that is fundamentally different from the vasculature of most peripheral tissues[65].

From a drug delivery perspective, the restrictive nature of the BBB arises from several interrelated functional features. First, the intercellular junctions between BMECs greatly limit passive paracellular movement of solutes[66]. Second, transcellular trafficking across the BBB is tightly controlled, allowing only selected endogenous molecules to enter the brain through specialized transport systems[67]. Third, endothelial cells express metabolic enzymes and active efflux transporters, which can degrade therapeutic molecules or pump them back into the circulation, thereby further reducing intracerebral exposure[68]. As a result, although some small molecules can partially access the CNS, most macromolecules, biologics, and nanoparticle-based systems cannot simply diffuse into the brain in therapeutically meaningful amounts[69].

These BBB properties are particularly relevant in the context of nanomedicine. While nanocarriers can improve drug stability, prolong circulation, and support multifunctional therapeutic design, they do not inherently possess efficient brain-penetrating capacity[70]. On the contrary, their size, surface properties, and interactions with biological interfaces often make them even more dependent on active transport mechanisms, transient barrier modulation, or alternative delivery routes. In other words, the challenge in PD is not merely to develop nanomedicine formulations, but to design nanomedicine systems that can interact with the BBB in a controlled, effective, and safe manner[71].

Another important consideration is that the BBB in PD should not be viewed as a completely static barrier. Aging, chronic neuroinflammation, vascular dysfunction, and disease progression may alter BBB integrity and transport behavior in a region- and stage-dependent manner[36]. Astrocyte activation, endothelial dysfunction, and neurovascular remodeling have all been implicated in BBB dysregulation in neurodegenerative conditions, including PD[72–74]. Although these changes may in some cases create transient opportunities for drug entry, they also introduce additional heterogeneity and uncertainty into delivery design and therapeutic evaluation[75]. Therefore, successful nanomedicine-based intervention in PD requires not only overcoming the BBB as a general barrier, but also accounting for its dynamic pathological context[76].

Taken together, the BBB remains the central biological constraint on brain delivery in PD. Its structural selectivity, tightly regulated transport behavior, and disease-related variability explain why many therapeutics fail to achieve adequate exposure in the target brain regions, even when they show promising pharmacological activity in principle[77,78]. This challenge has driven the development of 2 broad categories of nanomedicine-based delivery strategies: those designed to cross the BBB and those intended to bypass it. The following sections discuss these 2 approaches in detail.

5. Nanomedicine strategies for crossing the BBB

Given that the BBB remains the principal obstacle to brain delivery in PD, considerable effort has been devoted to the development of nanomedicine strategies capable of crossing this barrier. Unlike bypass approaches, these strategies seek to negotiate directly with the BBB by harnessing endogenous transport mechanisms, promoting vesicular translocation, or temporarily increasing barrier permeability. Their appeal lies in the potential to achieve brain delivery while preserving the anatomical integrity of the delivery route and avoiding more invasive

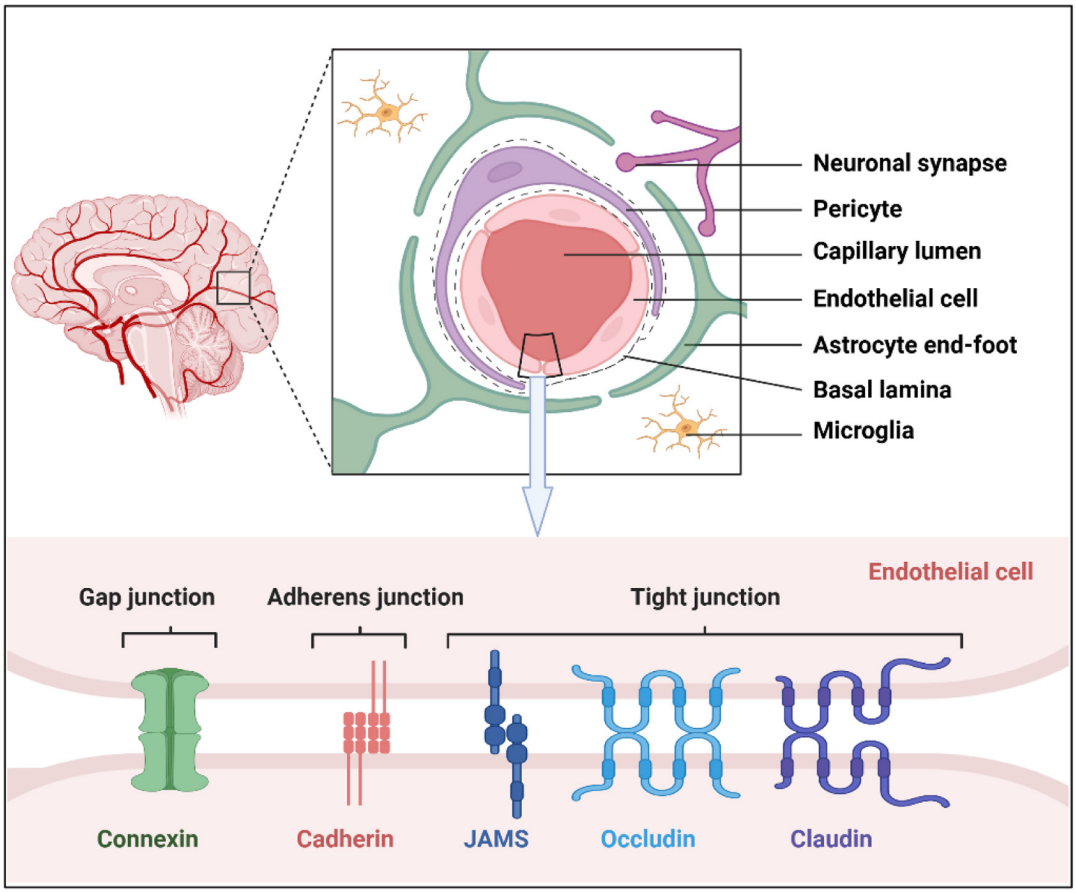


Figure 2. Structural organization of the BBB and the neurovascular unit. This schematic illustrates the cellular architecture of the BBB and the neurovascular unit. Brain microvascular endothelial cells form the vascular wall and are closely associated with the basement membrane, pericytes, astrocytic end-feet, neuronal elements, and microglia, which together contribute to BBB formation and maintenance. The lower panel highlights the major intercellular junctional complexes between adjacent endothelial cells, including tight junctions, adherens junctions, and gap junctions, with representative components such as claudin, occludin, junctional adhesion molecules, cadherins, and connexins.

procedures[17]. Based on their underlying principles, current approaches can be grouped into transport-mediated systems, adsorptive or biomimetic transcytosis strategies, and physically assisted BBB-opening technologies (Figure 3).

5.1 Carrier-mediated transport-based strategies

Carrier-mediated transport (CMT) is one of the major endogenous transport mechanisms that support nutrient exchange across the BBB. To meet the metabolic demands of the brain, brain endothelial cells express a variety of saturable and bidirectional transporters responsible for the uptake of essential small polar molecules, including glucose, amino acids, vitamins, fatty acids, and other nutrient-related substrates. These carriers recognize specific ligands and undergo conformational transitions that enable substrate translocation across the endothelial barrier. Based on this principle, nanomedicine platforms can be functionalized with transporter-recognizable substrates or substrate-mimicking moieties in an attempt to exploit these physiological transport systems and enhance brain delivery[79].

Compared with passive diffusion, CMT-based strategies are attractive because they rely on intrinsic BBB transport routes rather than nonspecific permeabilization. In principle, such approaches may improve brain entry while preserving barrier integrity and reducing the need for invasive intervention[9]. For PD therapy, this concept is especially relevant for cargos that cannot achieve sufficient intracerebral exposure in free form but may benefit from transporter-assisted entry when incorporated into a nanoplatform. In addition, because some endogenous transport systems are highly expressed at the BBB, they provide a biologically rational interface for the design of brain-targeted nanocarriers[65].

Several representative studies have explored this strategy. For example, a polymer containing choline- and acetylcholine-like moieties was reported to cross the BBB under the mediation of choline- and acetylcholine-related transport systems, thereby enabling the delivery of protein therapeutics into the CNS[80]. In another study, a gold nanoparticle-based composite nanovehicle loaded with plasmid DNA was modified with docosahexaenoic acid (DHA) and nerve growth factor (NGF). In this design, DHA was intended to facilitate BBB transport through interaction with fatty acid-related transport pathways, while NGF was further used to promote neuronal targeting after brain entry[81]. These examples illustrate how CMT-inspired nanodesign can be combined with secondary targeting elements to improve not only BBB interaction but also subsequent distribution toward disease-relevant cells.

Although CMT is conceptually attractive, its practical application still faces several key challenges. First, the number and transport capacity of endothelial carriers are inherently limited, and saturation and competition effects exist. This necessitates nanocarrier designs that balance high affinity with low endogenous interference. To this end, 1 can select carriers that are highly expressed on brain endothelial cells and possess relatively large transport cavities as targets, and employ nonnatural amino acid/sugar mimetics or allosteric modulators to avoid competition

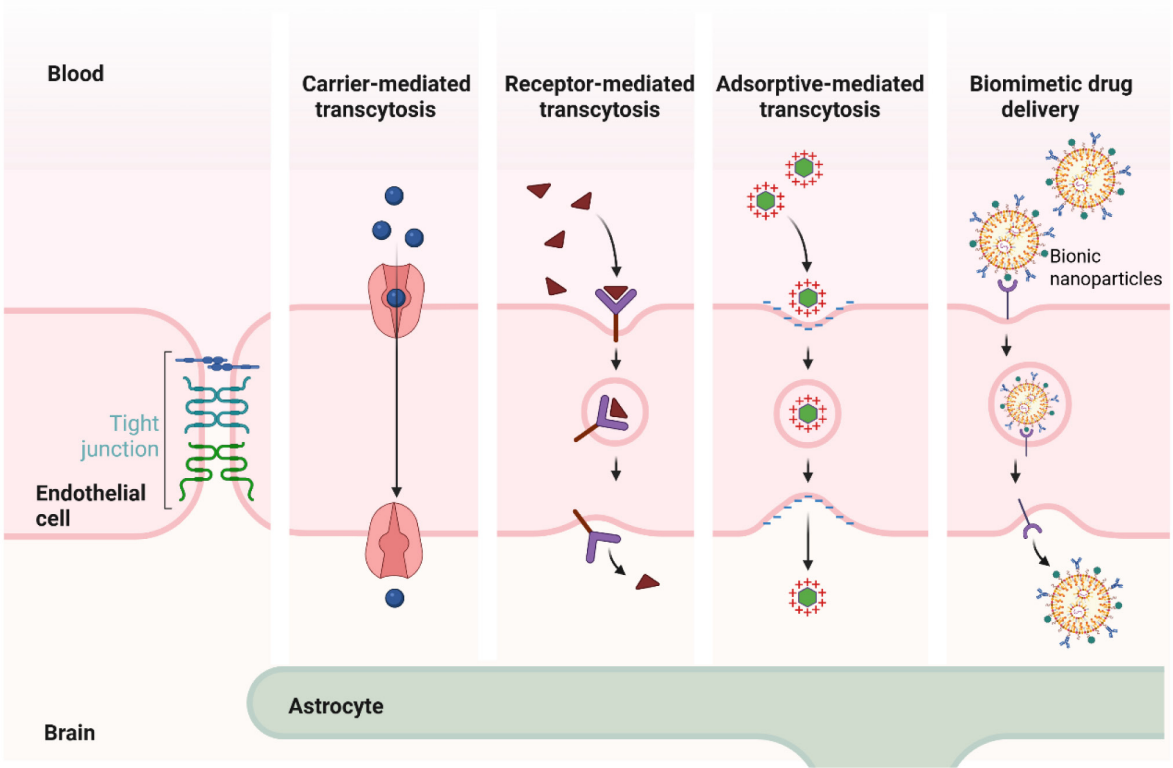


Figure 3. Major biological transport mechanisms for crossing the BBB. This schematic summarizes several representative biological pathways by which therapeutic agents or nanomedicines may traverse the BBB, including carrier-mediated transcytosis, receptor-mediated transcytosis, adsorptive-mediated transcytosis, and biomimetic drug delivery. Carrier-mediated transcytosis exploits endogenous solute transport systems to facilitate BBB passage. Receptor-mediated and biomimetic strategies rely on ligand-receptor interactions on the luminal surface of endothelial cells to trigger endocytosis and vesicular transcellular transport. Adsorptive-mediated transcytosis is driven by electrostatic interactions between positively charged nanomedicines and negatively charged components of the endothelial surface. Together, these mechanisms provide distinct routes for enhancing brain delivery across the BBB.

with natural substrates for the active site, thereby achieving selective delivery without sacrificing overall transport flux. Second, most carriers are naturally adapted to small-molecule substrates and exhibit limited compatibility with complex nanoplatforms; however, this can be addressed by multivalent ligand modification or biomimetic mineralization strategies to enhance apparent affinity, thereby improving the transport efficiency of larger-sized carriers. Furthermore, the heterogeneity of transporter expression across species, brain regions, and pathological conditions suggests that clinical translation should incorporate individualized assessment or imaging guidance[82–84]. Importantly, these challenges are not inherent flaws of CMT-based strategies, but rather drivers for innovation in precision nanoengineering. Compared with nonspecific permeabilization or invasive approaches, CMT offers a physiologically compatible and regulatable route for brain delivery, and with rational design, it still holds the potential to achieve efficient and low-toxicity brain-targeted delivery.

5.2 Receptor-mediated transport-based strategies

Receptor-mediated transport (RMT) remains one of the most intensively investigated routes for brain-targeted nanomedicine, largely because it harnesses endogenous endocytic and transcytotic machinery expressed on the luminal membrane of the BBB[85]. Unlike carrier-mediated systems, which are evolutionarily tuned for small nutrients, RMT exploits ligand-receptor recognition to trigger vesicular trafficking of macromolecular cargos, an attractive feature for delivering proteins, antibodies, nucleic acids, and multifunctional nanocarriers that otherwise show negligible free penetration into the brain[55]. In PD, this strategy gains additional relevance from the need to not only cross the BBB but also reach vulnerable dopaminergic neurons, a dual requirement that has spurred considerable innovation in ligand design and nanoplatform engineering.

A broad palette of ligands, including transferrin, lactoferrin, Angiopep-2, dopamine-related moieties, and RVG29-derived peptides, has been conjugated to nanoparticles to promote selective engagement with endothelial receptors[86,87]. Although each ligand-receptor pair has its own binding kinetics and tissue distribution profile, a common rationale underpins these designs: to enhance brain accumulation while, in many cases, conferring secondary neuronal tropism after extravasation[9]. This dual-targeting potential is particularly coveted in PD, where therapeutic efficacy depends on precise delivery to disease-relevant cell populations. Among the most widely explored are lactoferrin-modified systems, which benefit from the fact that lactoferrin receptors are present on both brain endothelium and neurons. For instance, a lactoferrin-functionalized platform that releases nitric oxide and paeoniflorin under near-infrared (NIR) stimulation successfully combined gas therapy with pharmacological intervention in a PD model[88]; Similarly, lactoferrin-decorated black phosphorus (BP) nanosheets loaded with paeoniflorin demonstrated favorable biocompatibility and brain-targeting performance[89]. Transferrin receptor-targeted carriers, by contrast, have been particularly valuable for macromolecular biologics, as exemplified by transferrin-modified liposomes delivering the anti-α-synuclein antibody SynO4, which achieved markedly higher antibody accumulation in brain cells than free antibody[90]. These cases illustrate that while the same RMT principle applies, the choice of ligand substantially influences the type of cargo that can be efficiently shuttled and the subsequent intracellular fate.

Beyond simple ligand decoration, recent work has pushed RMT toward multifunctional, stimuli-responsive architectures

that integrate BBB crossing with disease-microenvironment sensing. A ROS-responsive, carrier-free nanomedicine was designed to exploit dopamine receptor-mediated uptake, enabling BBB passage and neuronal internalization before releasing rasagiline mesylate and dopamine specifically in the oxidative PD milieu[91]. Angiopep-2-modified nanoparticles have been used for codelivery of rasagiline and the P-glycoprotein inhibitor tariquidar, achieving significantly enhanced brain targeting relative to free drug[92]. RVG29-based systems further expand the toolkit by recognizing nicotinic acetylcholine receptor-related targets on both endothelium and neurons. They have been employed for codelivery of miR-133b and curcumin to simultaneously mitigate α-synuclein pathology, attenuate neuroinflammation, and promote repair[93]. Notably, RVG29-functionalized red blood cell membrane-coated curcumin nanoparticles have shown prolonged circulation and reduced reticuloendothelial clearance, underscoring how RMT can be effectively merged with biomimetic coating strategies to enhance overall pharmacokinetic performance[94]. Collectively, these examples demonstrate that RMT is not a monolithic tactic but a flexible backbone onto which multiple layers of functionality, such as stimulus responsiveness, combination therapy, and immune evasion, can be grafted. Beyond therapeutic delivery, RMT has also been extended to diagnostic applications; for instance, a HClO-activatable NIR-IIb fluorescent probe (SQ6-RENps) was recently reported to cross the BBB via VHPKQHR peptide-mediated transport, enabling real-time monitoring of intracerebral hypochlorous acid levels to reflect PD severity and evaluate therapeutic responses[95].

Despite these advances, the clinical translation of RMT-based nanomedicines faces persistent hurdles that go far beyond the initial receptor-binding step. The most fundamental bottleneck is that binding does not equate to productive transcytosis: after endocytosis, the vast majority of nanoparticles are either sequestered in lysosomes for degradation or recycled back to the vascular lumen, with only a minute fraction successfully reaching the brain parenchyma. This low trafficking efficiency is compounded by competitive inhibition from endogenous ligands (eg, transferrin in serum) and receptor saturation at high nanomedicine doses, which collectively cause in vitro targeting performance to deteriorate sharply in vivo[96–98]. Moreover, the rapid adsorption of plasma proteins onto nanoparticle surfaces, forming a protein corona, can physically mask targeting ligands, further undermining receptor recognition and contributing to the frequent discrepancy between cell-based assays and animal results[99]. Target specificity poses another layer of difficulty: receptors such as the transferrin receptor are widely expressed in peripheral organs (liver, spleen), leading to off-target accumulation that not only reduces brain bioavailability but also raises systemic toxicity risks[100]. Receptor density, trafficking kinetics, and accessibility also vary across species, disease stages, and brain regions, making it perilous to extrapolate preclinical findings directly to human PD pathology[15,101]. Even multivalent ligand modification, while boosting apparent affinity, may alter nanoparticle size, surface charge, and pharmacokinetics in ways that impair extravasation and tissue penetration. Safety considerations further complicate the picture; antibody- or peptide-based ligands can elicit immunogenicity, and chronic administration may disrupt receptor homeostasis and compromise BBB integrity[102].

Addressing these challenges will require a coordinated, multipronged shift in design philosophy. Future research should move beyond the pursuit of high-affinity binding toward low-affinity, high-selectivity ligands that minimize competition and off-target effects, coupled with anti-protein-corona surface modifications to preserve targeting function in biological fluids. Enhancing lysosomal escape and intracellular trafficking, for instance via pH-responsive or fusogenic moieties, could significantly increase the fraction of internalized nanoparticles that undergo transcytosis. Equally important is the adaptation of RMT systems to pathological features, such as by designing ligands that recognize disease-upregulated receptors or by incorporating microenvironment-triggered release to ensure cargo deployment only at sites of active neurodegeneration[103–105]. Ultimately, the success of receptor-mediated strategies will depend not on a single breakthrough but on the synergistic optimization of ligand design, nanoparticle engineering, and a deeper understanding of BBB dynamics under disease conditions, a goal that demands iterative feedback between preclinical models and clinically relevant benchmarks.

5.3 Adsorptive and biomimetic transcytosis strategies

In addition to carrier- and receptor-mediated pathways, nanomedicine platforms may also cross the BBB through adsorptive or biomimetic interactions with the brain endothelium. These approaches are attractive because they do not rely exclusively on a single endogenous transporter or receptor. Instead, they seek to enhance BBB translocation by either increasing nonspecific but exploitable interactions with the endothelial surface or by endowing nanocarriers with biological interfaces that more closely resemble native cells or extracellular vesicles[106,107]. In the context of PD, such strategies are of particular interest because they can be integrated with multifunctional nanoplatform design and may offer broader flexibility for delivering diverse therapeutic cargos.

AMT is primarily driven by electrostatic interactions between positively charged carriers and negatively charged domains on the luminal surface of BBB endothelial cells[106]. The endothelial membrane contains anionic components, such as glycosaminoglycan-rich structures, that can promote the adsorption of cationic nanomaterials or macromolecular therapeutics. After this initial surface interaction, the adsorbed carriers may undergo endocytic uptake, intracellular vesicular trafficking, and subsequent exocytotic release on the abluminal side, thereby completing transcytosis across the barrier[108]. From a design perspective, AMT can be promoted by using cationic polymers, surface charge engineering, cell-penetrating peptides, or other positively charged surface modifications[79,109]. Compared with highly specific receptor-targeted systems, AMT may provide a more generally accessible route for BBB interaction, particularly for nanosystems that are difficult to functionalize with precise ligand-receptor pairs.

Representative studies suggest that AMT-based concepts can be combined with more complex vesicular formulations. For example, a delivery system based on small apoptotic bodies was used to encapsulate antisense oligonucleotide-containing nanocomplexes, taking advantage of membrane-associated interactions with BBB endothelial glycocalyx components to facilitate endothelial uptake and transcytosis[33]. This example highlights an important feature of AMT-inspired strategies: electrostatic adsorption alone is often not the whole story, and successful BBB transfer may depend on the coordinated contribution of surface charge, membrane composition, and vesicular trafficking behavior. Thus, AMT should be understood less as a single mechanism and more as a design principle for enhancing endothelial interaction and transcellular transport.

Biomimetic transcytosis strategies take this concept further by equipping nanocarriers with cell-derived or cell-like interfaces to improve circulation, immune evasion, BBB interaction, and downstream targeting. Over the past decade, biomimetic delivery systems have attracted growing attention because cell membranes, extracellular vesicles, and related biological coatings can endow nanoparticles with functions that are difficult to reproduce using purely synthetic materials[110]. Depending on the source of the membrane or vesicle, these functions may include prolonged systemic circulation, reduced reticuloendothelial clearance, inflammatory tropism, neuronal affinity, or enhanced

compatibility with the BBB[111,112]. For PD therapy, such features are particularly appealing because the disease requires not only access to the CNS, but often selective action within neuroinflammatory or neurodegenerative microenvironments.

Several membrane-based biomimetic strategies have been explored in PD models. Neural stem cell membrane-coated nanoparticles have been reported to improve the targeted delivery of antisense oligonucleotides while also supporting endogenous neural stem cell recruitment for neuronal repair[113]. Red blood cell membrane-based systems have been used to prolong circulation and reduce immune clearance, and when combined with stimulus-responsive cores, they can further support controlled therapeutic release after brain delivery[114]. Neuronal membrane-coated nanoparticles have also been developed to target activated microglia and modulate neuroinflammation, whereas macrophage membrane-based nanosystems may exploit inflammation-associated homing features while carrying mitochondria-protective or antiinflammatory payloads[115]. In addition, engineered exosome-like systems have shown considerable promise because their intrinsic intercellular communication properties and nanoscale dimensions make them attractive vehicles for RNA drugs, small molecules, and combination formulations. For instance, exosome-based hybrid systems have been designed for the codelivery of SNCA-targeting siRNA and curcumin, aiming to simultaneously reduce α-synuclein pathology and regulate immune activation in PD-related settings[116]. A recent study further developed a biomimetic nanosystem (Cur-Exo@Pt-PB) consisting of curcumin-derived exosomes encapsulating platinum-Prussian blue nanozymes, which effectively traverses the BBB by modulating protein corona composition to evade immune clearance while synergistically exerting antioxidant effects and inducing microglial M2-polarized antiinflammatory responses, thereby achieving effective therapy for PD[117].

Despite their conceptual appeal, adsorptive-mediated and biomimetic transcytosis strategies face distinct limitations. In AMT-based systems, increased positive charge can enhance BBB interaction but may also increase nonspecific binding, serum protein adsorption, cytotoxicity, and off-target uptake. The resulting gain in endothelial association does not always translate into efficient or selective delivery to the brain parenchyma[118]. Biomimetic systems, while often offering improved biological performance, come at the cost of greater complexity. First, manufacturing scalability and batch-to-batch consistency remain fundamental obstacles, as most biomimetic nanoplatforms are synthesized at the milligram scale using nonstandardized laboratory procedures that are often incompatible with large-scale production[119]. Second, inadequate storage and transport stability represent another critical issue, since membrane proteins and lipids are susceptible to denaturation, oxidation, aggregation during storage, imposing stringent requirements on cold-chain management[120]. Third, immunogenicity risks cannot be overlooked; although biomimetic strategies aim to evade immune clearance through "self" recognition, the introduction of exogenous biological materials may still trigger unintended immune activation, and long-term biosafety data remain largely lacking[121]. Moreover, although exosomes and membrane-coated nanoparticles are often described as naturally brain-targeting, their in vivo trafficking and BBB transport mechanisms are not always fully understood or quantitatively validated[122]. From a clinical translation perspective, no biomimetic nanoplatform has yet been approved for PD treatment, largely due to the absence of harmonized regulatory guidelines specifically tailored to such complex nanomedicines, insufficient systematic evaluation of biodistribution and pharmacokinetics, and interspecies differences that make it difficult to replicate preclinical efficacy in humans[43]. Consequently, while adsorptive and biomimetic strategies expand the design space of BBB-crossing nanomedicine for PD, their successful translation will depend on achieving a workable balance between biological sophistication, mechanistic clarity, safety, and manufacturability. Future research should focus on developing scalable and standardized manufacturing processes, establishing robust quality control systems, and conducting thorough assessments of long-term biosafety and immunogenicity.

5.4 Focused ultrasound-assisted BBB opening

Focused ultrasound (FUS) represents a distinct class of BBB-crossing strategies because it does not primarily rely on ligand-mediated interaction with endothelial transport systems. Instead, it uses externally applied acoustic energy to locally and transiently modulate BBB permeability, thereby creating a physical window for the entry of therapeutic agents into the brain[123]. In the field of PD, FUS has attracted growing interest not only because of its established use in image-guided neuromodulatory or ablative procedures, but also because its combination with intravenously administered microbubbles has opened a new avenue for noninvasive, region-specific brain delivery of macromolecules, gene vectors, and nanosystems[124].

The therapeutic application of FUS in PD initially centered on thermal ablation. By focusing ultrasound energy onto defined deep brain targets, such as the subthalamic nucleus or related motor circuits, FUS can induce localized tissue heating and thereby alleviate symptoms such as tremor[125–127]. However, from a drug delivery perspective, the more transformative development has been the emergence of microbubble-assisted focused ultrasound (MB+FUS). In this approach, systemically administered microbubbles oscillate in the ultrasound field within the targeted cerebral vasculature, generating mechanical effects at the neurovascular interface. These effects can temporarily loosen endothelial tight junctions and enhance vesicular transport activity, leading to a reversible increase in BBB permeability[128]. Compared with systemic chemical modulation or invasive local administration, MB+FUS offers several important advantages, including regional precision, temporal controllability, and the possibility of repeated noninvasive intervention[129].

However, the physical window opened by ultrasound alone does not guarantee efficient delivery of free therapeutic agents. Even in the region of barrier opening, free drugs often fail to cross effectively or are rapidly cleared from the circulation. The introduction of nanocarriers significantly improves this process. Nanocarriers can encapsulate macromolecules, nucleic acids, or unstable drugs into particles of appropriate size, enabling them to pass through the transient channels induced by ultrasound, while also prolonging circulation time and reducing peripheral organ exposure[130,131]. Surface modification with targeting ligands enhances local accumulation, and environment-responsive designs allow triggered release at the lesion site. Together, these features reduce systemic toxicity and protect the cargo from enzymatic degradation[132]. Furthermore, nanoplatforms can carry gene-editing tools or enable combination therapy, greatly expanding the repertoire of deliverable drugs[133]. Thus, the value of nanocarriers lies in transforming the local opening effect of ultrasound into meaningful therapeutic benefit in the brain, rather than serving merely as an auxiliary tool for barrier traversal.

These features make MB+FUS particularly attractive for PD therapies that are pharmacologically promising but delivery-limited. Neurotrophic factors such as GDNF and brain-derived neurotrophic factor have long been recognized for their ability to support dopaminergic neuron survival and repair, yet their clinical application has been severely restricted by insufficient brain delivery. To address this problem, FUS-based systems have been developed to combine circulating carriers with ultrasound-triggered BBB opening. For example, a microbubble–liposome complex loaded with neurotrophic factors was reported to achieve targeted intracerebral delivery after FUS irradiation, resulting in significant behavioral and pathological

improvement in PD model mice (Figure 4A). This type of strategy illustrates the value of FUS as a delivery amplifier: rather than replacing the nanocarrier, it enables a locally gated entry process that can enhance the effectiveness of otherwise poorly brain-penetrant therapeutics[134].

Magnetic resonance-guided focused ultrasound (MRgFUS) has further improved the translational potential of this approach by integrating real-time imaging with precisely controlled acoustic targeting. In a phase I clinical study involving PD patients with GBA1 mutations, MRgFUS combined with microbubbles was used to transiently open the BBB in the putamen in order to improve the intracerebral delivery of glucocerebrosidase (GCase) enzyme therapy. Preliminary findings suggested that the procedure was feasible and safe, with BBB integrity largely restored within 24 h and no evidence of long-term disruption (Figure 4B–D). Although still early, such studies provide important clinical proof-of-principle that FUS-assisted BBB opening may become a realistic platform for enabling brain delivery of biologics in PD[135].

The main challenge for FUS-assisted BBB opening is not proof of concept, but parameter control, reproducibility, and long-term neurovascular safety. Its delivery outcome depends heavily on ultrasound parameters such as acoustic pressure, pulse duration, frequency, exposure time, and cavitation behavior, all of which must be optimized to balance delivery efficiency against tissue safety[136]. In addition, microbubble formulation, circulation stability, and acoustic responsiveness can substantially influence treatment reproducibility. Repeated BBB opening also raises important questions regarding cumulative neurovascular effects, inflammatory responses, and long-term safety, particularly in elderly or neurodegenerative populations[137,138]. Therefore, FUS should be viewed not simply as a BBB-opening technique, but as a highly promising yet parameter-sensitive enabling technology whose clinical value in PD will depend on careful standardization, imaging guidance, and integration with appropriately designed therapeutic cargos.

5.5 Photothermal strategies for BBB modulation and brain delivery

Photothermal strategies represent another physically assisted approach for enhancing brain delivery across the BBB. Unlike transporter- or receptor-dependent nanomedicine systems, these approaches rely on photothermal agents that absorb NIR light and convert optical energy into localized heat, thereby transiently increasing BBB permeability and facilitating drug entry into the brain[139,140]. In the context of PD, photothermal-assisted delivery has attracted interest because it combines relatively low invasiveness with spatial controllability and can be integrated with multifunctional nanoplatform design. Notably,

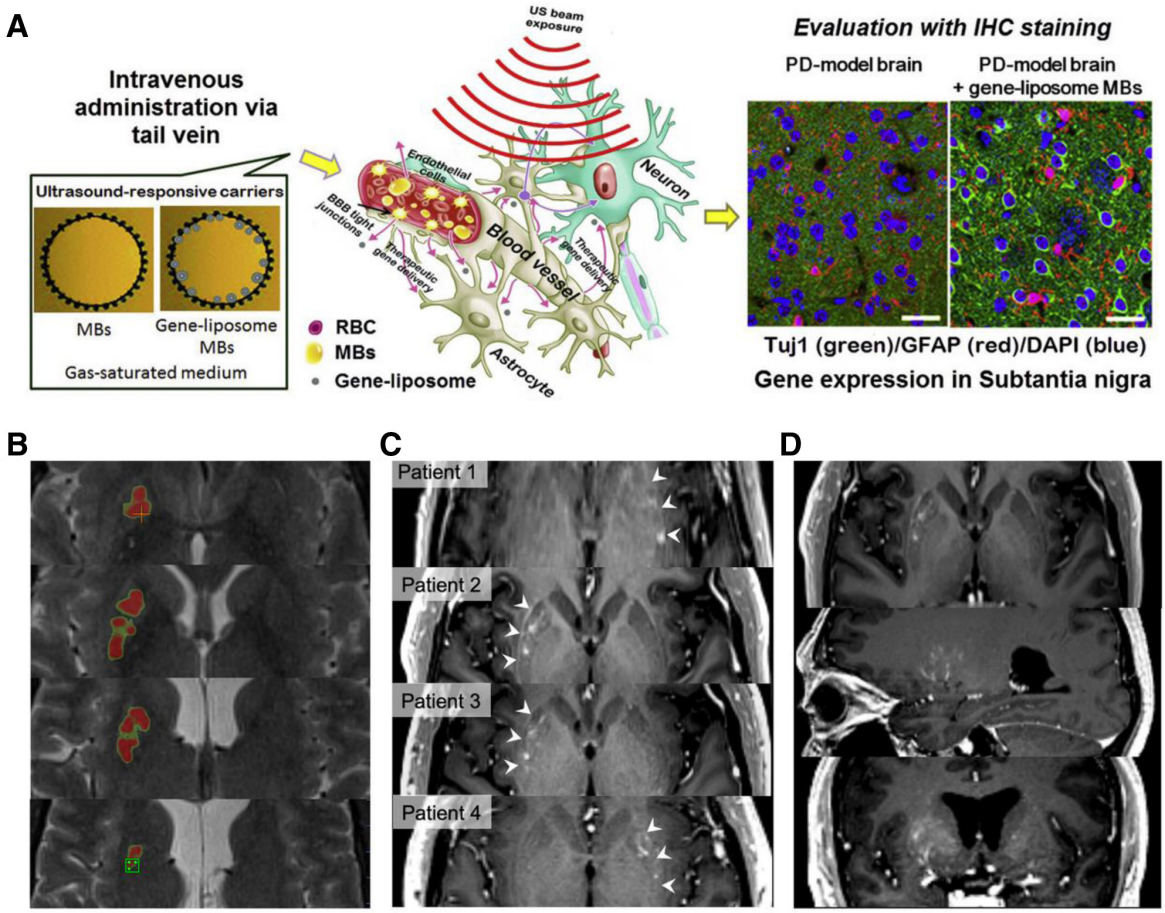


Figure 4. Focused ultrasound-assisted BBB opening for brain delivery. (A) Schematic illustration of intravenous administration of gene-liposome microbubbles followed by focused ultrasound exposure to induce localized BBB opening and facilitate intracerebral gene delivery. Immunohistochemical staining of PD-model brains shows gene expression in the substantia nigra after treatment with gene-liposome microbubbles[134]. Copyright 2020, Elsevier B.V. (B) Representative T2-weighted MRI acquired during an MR-guided focused ultrasound (MRgFUS) procedure, with the colormap indicating the relative ultrasound dose delivered to the putamen. (C) Contrast-enhanced T1-weighted MRI from individual patients showing gadolinium extravasation in the sonicated putamen (arrows), indicating localized BBB disruption. (D) Representative contrast-enhanced T1-weighted MRI in orthogonal planes illustrating the three-dimensional configuration of the BBB opening [135]. Copyright 2022, The Authors. Movement Disorders published by Wiley Periodicals LLC on behalf of the International Parkinson and Movement Disorder Society.

the photothermal agent itself is typically a nanomaterial (eg, BP nanosheets and polydopamine nanoparticles). Beyond serving as the energy converter, the nanocarrier encapsulates and protects the therapeutic cargo, enables brain targeting through surface modification, and can achieve stimulus-responsive drug release. This dual or triple functionality is difficult to replicate with small-molecule photothermal agents or with free drugs alone[89]. Rather than serving solely as a carrier property, the photothermal effect itself becomes an active component of the delivery process[141].

The effectiveness of this strategy depends largely on the properties of the photothermal agent. Ideally, photothermal materials used for BBB modulation should exhibit strong NIR absorption, high photothermal conversion efficiency, good photostability, biodegradability, and acceptable biocompatibility[142,143]. Upon NIR irradiation, localized heating at the vascular interface may disrupt endothelial integrity or transiently increase barrier permeability, thereby enabling the delivery of therapeutic cargos that would otherwise show poor brain penetration. At the same time, this mode of delivery also offers the possibility of coupling BBB modulation with stimulus-responsive drug release, which is particularly attractive for multifunctional nanosystems in PD[114,142].

BP-based nanomaterials are among the most widely investigated photothermal platforms in this context because of their high photothermal conversion efficiency and biodegradability[144]. For example, polyethylene glycol (PEG)-modified BP nanosheets loaded with matrine were developed as a multifunctional nanomedicine for PD (Figure 5A). In this system, NIR-triggered photothermal effects promoted BBB penetration, while matrine contributed antioxidant activity through regulation of oxidative stress-related pathways (Figure 5B). As a result, the combined platform was reported to exert synergistic antiparkinsonian effects through ROS scavenging and reduction of α-synuclein aggregation[145]. This example illustrates how photothermal assistance can be integrated with a therapeutic cargo that is pharmacologically relevant but otherwise limited by insufficient brain exposure.

Other photothermal nanoplatforms have extended this concept by combining BBB modulation with gene-related or mitochondria-protective therapies. A representative example is the MgOp@PPLP system, which uses MgO nanoparticles as a core, polydopamine (PDA) as a photothermal framework, and an anti-SNCA plasmid as a therapeutic component, with additional PEG, puerarin, and lactoferrin modifications to improve hydrophilicity, antioxidant activity, and brain targeting (Figure 5C). Under 808 nm NIR irradiation, the PDA component generated a controlled temperature increase that promoted BBB permeability and enhanced brain delivery of the nanomedicine (Figure 5D)[146]. Similarly, a zeolitic imidazolate framework 8-coated Prussian blue nanocomposite loaded with quercetin has been developed to exploit the photothermal properties of Prussian blue for BBB modulation while simultaneously delivering a neuroprotective small molecule. These studies highlight the versatility of photothermal approaches, which can support the delivery of small molecules, nucleic acid cargos, and multifunctional combination systems[142].

Despite these promising results, photothermal BBB modulation remains at a relatively early stage compared with more established approaches such as FUS-assisted barrier opening. One important limitation is the restricted tissue penetration depth of light, which constrains the efficiency and clinical practicality of NIR-triggered strategies, especially for deep brain targets relevant to PD[147]. In addition, achieving a therapeutically useful increase in BBB permeability without inducing excessive endothelial damage or off-target thermal injury requires careful control of irradiation parameters and photothermal material properties. The long-term biosafety, reproducibility, and spatial precision of these systems also remain to be fully established[148]. Therefore, photothermal strategies should currently be viewed as an innovative but still developing class of BBB-modulating technologies, with particular value as multifunctional nanomedicine platforms rather than as mature standalone solutions for PD brain delivery.

6. Nanomedicine strategies for bypassing the BBB

In contrast to BBB-crossing approaches, bypass strategies seek to reduce dependence on transvascular transport across the classical BBB by exploiting alternative anatomical routes or local delivery methods. Rather than negotiating directly with endothelial transport systems or transiently modulating barrier permeability, these approaches attempt to access the CNS through pathways such as the nasal cavity, meningeal-associated routes, or direct intracranial administration[149–151]. In PD, bypass strategies are particularly attractive for therapeutic cargos that are difficult to deliver efficiently through systemic circulation, including macromolecules, nucleic acids, and other formulations that require higher local exposure. At the same time, bypassing the BBB does not eliminate the challenges of brain delivery; instead, it shifts the main constraints toward factors such as delivery flux, regional distribution, repeatability, invasiveness, and clinical feasibility[152,153]. Based on these principles, current nanomedicine-based bypass strategies can be broadly categorized into intranasal delivery, meningeal-associated pathways, skull–meninges-related routes, and convection-enhanced or other local intracranial delivery approaches.

6.1 Intranasal delivery

Intranasal delivery is one of the most extensively investigated strategies for bypassing the BBB in brain-targeted therapy. Its central appeal lies in the possibility of delivering therapeutic agents from the nasal cavity to the CNS through direct anatomical connections, thereby reducing reliance on systemic circulation and classical transvascular BBB transport. Compared with oral or parenteral administration, intranasal delivery offers several potential advantages, including noninvasiveness, ease of administration, relatively rapid onset, and the possibility of limiting peripheral exposure. In PD, these features are particularly attractive for therapeutic agents that require repeated dosing or that exhibit insufficient brain exposure after conventional administration[19,154].

The nose-to-brain transport of drugs is thought to occur mainly through direct pathways associated with the olfactory and trigeminal systems. After deposition on the upper nasal mucosa, therapeutic agents may access the olfactory bulb and then distribute to deeper brain regions along olfactory-associated routes or reach the brainstem and other CNS areas through trigeminal nerve-related pathways (Figure 6A)[155,158]. Additional contribution from perineural or cerebrospinal fluid-adjacent spaces has also been proposed[155]. Although part of the administered dose may still enter the systemic circulation through nasal capillaries, the principal value of intranasal delivery lies in its capacity to provide a more direct route to the brain and potentially improve intracerebral exposure while reducing systemic side effects[159].

However, its practical performance is strongly constrained by multiple anatomical and physiological barriers within the nasal cavity. The nasal mucosa imposes multiple barriers, including mucus entrapment, epithelial resistance, local enzymatic degradation, mucociliary clearance, and the limited accessible area of the olfactory region. These factors can substantially reduce drug retention, absorption, and reproducibility of delivery to the brain. Nanocarriers substantially improve the performance of intranasal delivery by addressing multiple physiological barriers[19]. They can: (i) enhance mucosal penetration through

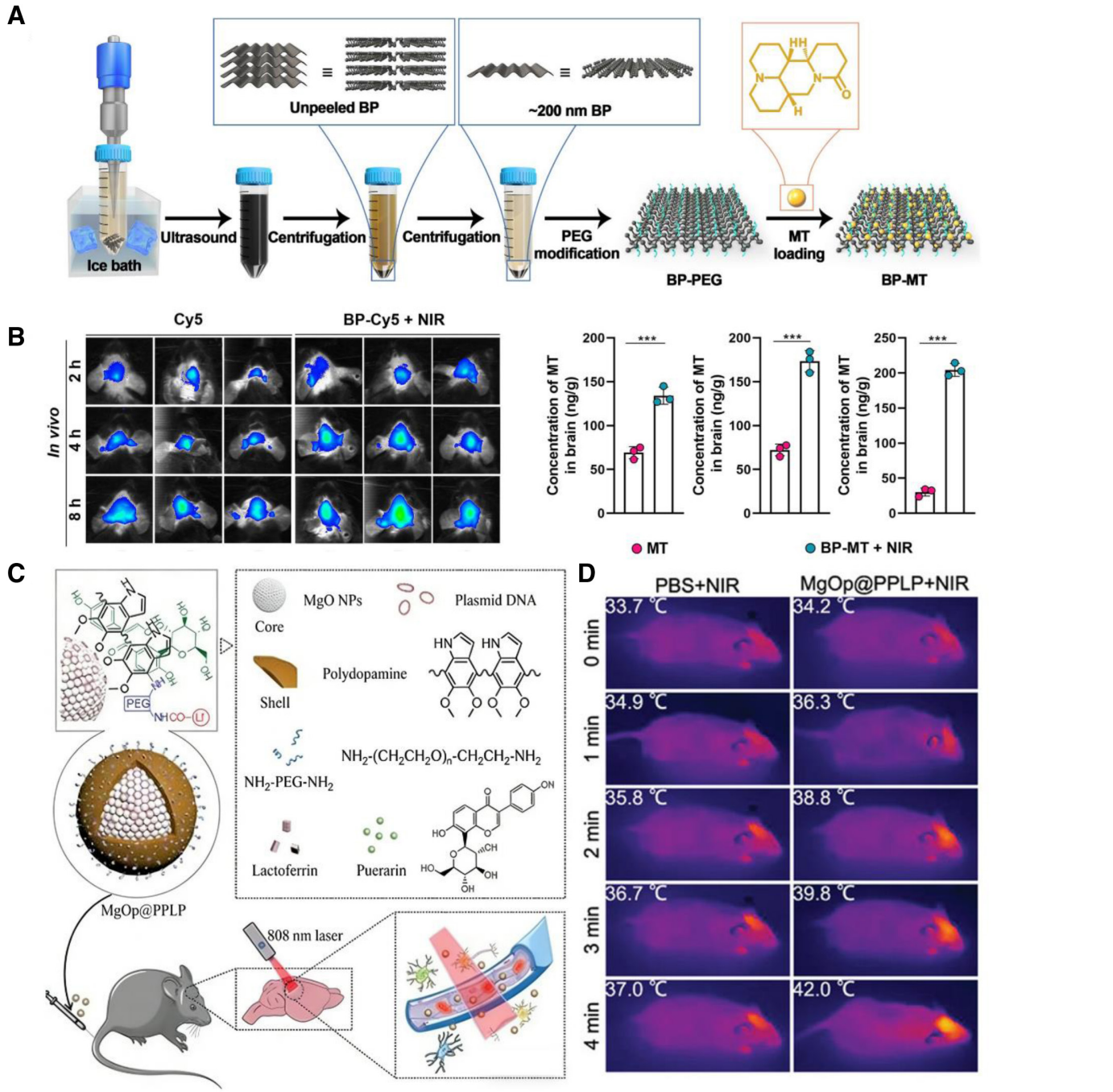


Figure 5. Photothermal-assisted nanomedicine for BBB modulation and brain delivery. (A) Schematic illustration of the preparation of the black phosphorus-based multifunctional nanoplatform BP-MT. (B) In vivo fluorescence imaging of C57BL/6 mice after administration of free Cy5 or BP-Cy5 with near-infrared (NIR) irradiation, together with quantitative analysis of matrine (MT) accumulation in the brain at 2, 4, and 8 h after treatment with free MT or BP-MT plus NIR irradiation ($n = 3$). Compared with the MT group: $P < 0.05$, $^{*}P < 0.01$, and $^{**}P < 0.001$[145]. Copyright 2022, Elsevier B.V. All rights reserved. (C) Schematic illustration of the synthesis of MgOp@PPLP and its NIR-triggered therapeutic procedure. (D) Representative infrared thermal images of mice exposed to 808 nm laser irradiation (0.8 W/cm^2) after administration of PBS or MgOp@PPLP[146]. Copyright 2022, Wiley-VCH GmbH.

surface charge or mucoadhesive polymers; (ii) protect encapsulated drugs from enzymatic degradation in the nasal cavity; (iii) prolong residence time by avoiding rapid mucociliary clearance; and (iv) provide sustained or controlled release after reaching the olfactory epithelium. By contrast, free drugs administered intranasally often suffer from poor absorption, rapid clearance, and low bioavailability. Thus, the value of nanomedicine in intranasal delivery is not merely in the route itself, but in the ability of nanocarriers to overcome the inherent limitations of the nasal mucosa[154,160,161]. Accordingly, current efforts to improve intranasal delivery have focused on 3 closely related aspects: formulation design, cargo optimization, and device engineering[161].

A representative example is an in situ gel nasal spray based on a lyotropic liquid crystal system for codelivering levodopa and epigallocatechin gallate. This formulation remains a low-viscosity precursor before administration, which facilitates

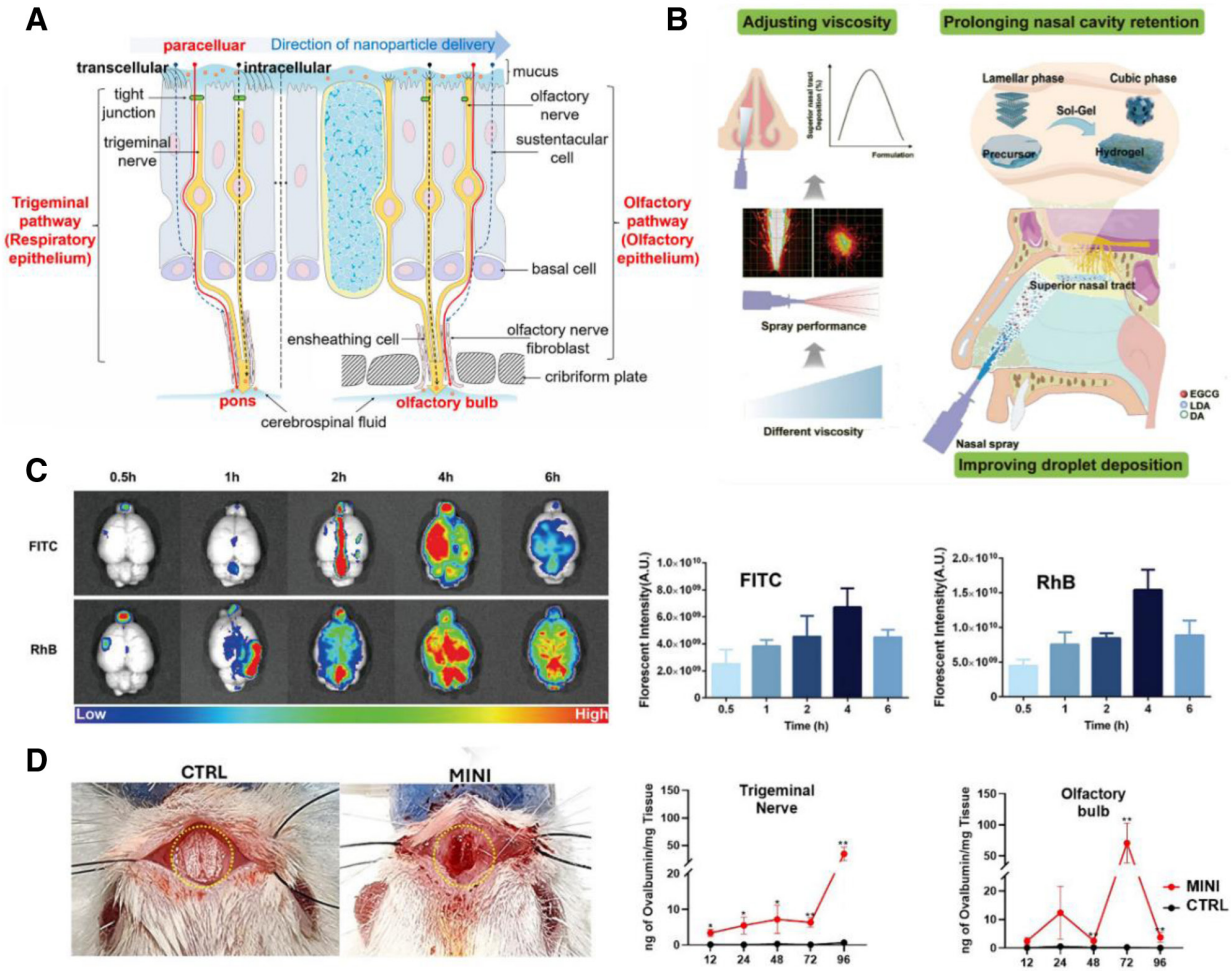


Figure 6. Intranasal nanomedicine delivery to the brain. (A) Schematic illustration of the major nose-to-brain transport pathways for nanoparticles, including trigeminal and olfactory routes [155]. Copyright 2023, American Chemical Society. (B) Schematic illustration of an in situ gel nasal spray designed for nose-to-brain delivery in a PD model. By adjusting formulation viscosity and inducing sol–gel phase transition after administration, this strategy improves upper nasal cavity deposition and prolongs mucosal retention to facilitate the codelivery of multiple drugs. (C)Representative whole-brain fluorescence imaging and semiquantitative analysis of surrogate drug distribution following intranasal administration of a lyotropic liquid crystal (LLC)-based in situ gel spray. Fluorescent probes, fluorescein isothiocyanate (FITC) and rhodamine B (RhB), were employed as surrogates for levodopa (LDA) and epigallocatechin gallate (EGCG), respectively[156]. Copyright 1999–2026, John Wiley & Sons, Inc. or related companies. (D) Schematic and representative images of a minimally invasive nasal infusion (MINI) strategy using a programmable infusion pump for intranasal delivery in mice. Quantification of ovalbumin levels in the trigeminal ganglion and olfactory bulb demonstrates enhanced regional brain delivery compared with control treatment [157]. Copyright 2024, The Authors

atomization, but rapidly undergoes a sol–gel transition after reaching the olfactory mucosa, thereby forming a mucoadhesive depot that prolongs residence time and improves local retention (Figure 6B). By optimizing rheological behavior and deposition characteristics, this system was designed to preferentially target the upper nasal cavity, where olfactory nerve-associated transport is most relevant (Figure 6C). Such a strategy illustrates how nanostructured formulations can improve not only drug stability and residence, but also spatial delivery precision within the nasal cavity[156].

Other nanomedicine-based intranasal approaches further demonstrate the versatility of this route. Carrier-free self-assembled nanodrugs based on quercetin and PEG, as well as solid lipid nanoparticles encapsulating geraniol–ursodeoxycholic acid conjugates, have both been reported to enhance nose-to-brain delivery and produce neuroprotective effects in PD-related models. In addition, a smart biomimetic nanoplatform based on kudzu-derived exosomes (hPH-RNPEC) has been developed, which, upon intranasal administration, can penetrate the nasal mucosa, home to inflammatory sites, and achieve dual targeting of neurons and microglia. It codelivers miRNA and curcumin to synergistically alleviate mitochondrial damage and neuroinflammation, thereby remodeling the brain microenvironment in PD and promoting neural repair[162]. These examples suggest that intranasal nanomedicine is not limited to reformulating classical drugs, but may also serve as a flexible platform for antioxidant, antiinflammatory, and multitarget therapeutic strategies relevant to PD pathology[163,164].

In addition to formulation optimization, device innovation is increasingly recognized as a key determinant of intranasal delivery performance[165]. One notable example is the minimally invasive nasal infusion strategy, which combines transnasal surgical access with a programmable infusion system to achieve controlled drug administration to the submucosal region of the olfactory mucosa. In experimental studies, this approach enabled efficient delivery of a model protein to multiple brain regions while maintaining very low peripheral blood levels, highlighting the importance of administration precision in improving the reliability of nose-to-brain transport (Figure 6D)[157]. Although such methods are more intervention-intensive than conventional nasal sprays, they underscore a critical point: successful intranasal brain delivery depends not only on the nanocarrier itself, but also on where and how the formulation is deposited.

Overall, intranasal delivery represents a highly attractive BBB-bypassing strategy for PD because it offers a nonvascular route to the brain and is well suited to repeated administration. However, its actual performance depends on overcoming fundamental constraints in nasal deposition, mucosal retention, transport flux, and regional distribution[166,167]. Thus, the future of intranasal nanomedicine in PD is likely to depend on the coordinated development of advanced formulations and precision delivery devices, rather than on carrier design alone.

6.2 Meningeal lymphatic-associated delivery pathways

Meningeal lymphatic-associated delivery pathways have emerged as a novel and conceptually important route for bypassing the BBB. For a long time, the CNS was regarded as largely isolated from classical lymphatic drainage; however, the discoveries of the glymphatic system and meningeal lymphatic vessels (MLVs) have substantially revised this view[168,169]. It is now understood that cerebrospinal fluid and interstitial solutes can be exchanged and cleared through perivascular and meningeal lymphatic networks, ultimately draining toward the deep cervical lymph nodes[170,171]. This anatomical and functional organization establishes a "brain–lymph–immune" axis that connects CNS fluid homeostasis, waste clearance, and immune surveillance, while also suggesting a previously underappreciated route for drug and nanoparticle trafficking to the brain[173,174].

As an anatomical bypass, the MLV pathway allows therapeutic agents to reach the CNS without crossing the classical BBB. In principle, free drugs, antibodies, or even small molecules can enter this pathway after appropriate administration (eg, cervical subcutaneous injection). However, this route alone suffers from inherent limitations: free molecules are rapidly degraded by enzymes in the interstitial fluid and lymphatic vessels, they are easily cleared by phagocytic cells in lymph nodes, and they cannot achieve sustained release or codelivery of multiple agents. Therefore, simply using the MLV pathway as a passive conduit does not guarantee efficient and safe brain delivery[175].

Nanomedicine addresses these limitations by providing distinct added value that differentiates a nanocarrier-based approach from generic CNS delivery along the MLV route. First, encapsulation protects labile biologics from enzymatic degradation, allowing them to survive the journey through the lymphatic network[175,176]. Second, nanocarriers can be engineered with surface ligands or membrane coatings to actively evade phagocytic clearance by immune cells within the lymph nodes, thereby improving transport efficiency and prolonging exposure[177]. Third, nanoparticles enable codelivery of multiple therapeutic agents in a single formulation, which is difficult to achieve with free drugs[178]. Fourth, the nanocarrier itself can contribute therapeutic functions beyond passive cargo transport, such as ROS scavenging, immunomodulation, or repair of dysfunctional MLVs[18]. Consequently, while the MLV route is an anatomical bypass, nanomedicine transforms it from a passive clearance pathway into an actively engineerable delivery and therapeutic platform.

Several representative studies support this concept. In a PD mouse model, cervical subcutaneous administration of $Cu_{2-x}Se$ nanoparticles was reported to repair MLV dysfunction induced by α-synuclein preformed fibrils and to improve behavioral and pathological phenotypes. Mechanistically, these nanoparticles were associated with upregulation of VEGF-C/VEGFR3 signaling, promotion of lymphangiogenesis, and restoration of meningeal lymphatic drainage. Such findings suggest that MLV-targeted nanomedicine may serve not only as a delivery route, but also as a therapeutic strategy aimed at correcting disease-related lymphatic impairment[18].

Biomimetic designs have further expanded the potential of this pathway. Because immune cell-rich lymphatic environments may promote nanoparticle clearance, membrane-camouflaged systems have been developed to improve transport efficiency and biological performance. For example, natural killer cell membrane-coated curcumin-loaded liposomes were reported to enhance delivery through the MLV-associated route while simultaneously reducing phagocytic clearance, scavenging ROS, and adsorbing α-synuclein[177]. In another study, an engineered hybrid membrane-coated nanoparticle combining copper–selenium nanomaterials with fused neuronal and macrophage-derived membrane components was used after cervical subcutaneous injection to target the brain through meningeal lymphatic pathways. The resulting system functioned both as a delivery vehicle and as an immunomodulatory nanoplatform, reducing inflammatory signaling and improving pathological outcomes in PD models[172].

This route may also offer practical advantages for reformulating existing therapies. One study encapsulated levodopa into tannic acid/polyvinyl alcohol nanoparticles and delivered it via the MLV-associated pathway, reporting reduced peripheral adverse effects together with improved central dopaminergic outcomes[179]. Such results are noteworthy because they suggest that meningeal lymphatic-associated delivery may not be limited to novel biological drugs or advanced nanoplatforms, but may also provide a means of improving the therapeutic index of established PD medications.

At present, MLV-associated brain delivery is best regarded as an emerging and still-evolving strategy rather than a fully established translational route. The exact transport dynamics, quantitative delivery efficiency, anatomical selectivity, and reproducibility of this route are not yet fully established, especially in larger animals and humans. In addition, the relationship between nanoparticle transport through lymphatic-associated pathways and final distribution within the brain parenchyma remains incompletely defined[180]. Therefore, meningeal lymphatic-associated delivery should currently be viewed as a highly promising but still developing bypass strategy, with particular value in expanding the conceptual landscape of brain-targeted nanomedicine and potentially linking drug delivery to restoration of CNS lymphatic homeostasis.

6.3 Skull–meninges vascular or microchannel-associated pathways

In addition to more established BBB-bypassing routes such as intranasal delivery and meningeal lymphatic-associated pathways, recently identified skull–meninges vascular or microchannel-associated structures have introduced a new conceptual framework for brain-targeted delivery. These channels connect the calvarial bone marrow with the meninges and appear to function as specialized conduits for communication between extracranial hematopoietic niches and the CNS border environment[181,182]. Under physiological conditions, they are thought to support the trafficking of immune cells from the skull bone marrow to the dura mater and thereby participate in meningeal immune surveillance. In pathological settings, these channels may also mediate bidirectional signaling between injured brain tissues and cranial bone marrow compartments, potentially guiding immune cell recruitment to sites of CNS damage[183].

From a drug delivery perspective, this anatomical connection is intriguing because it may provide an alternative route for transporting therapeutic systems toward CNS border regions without relying on classical transvascular passage across the BBB. Building on this concept, researchers have proposed a skull bone marrow–meningeal channel delivery strategy in which drug-loaded nanoparticles are introduced directly into the calvarial bone marrow cavity. After local uptake by endogenous immune cells, these therapeutic cargos may then be conveyed through the skull–meninges channel network toward lesion-associated meningeal or parenchymal regions[20,182]. This route is particularly notable because it does not simply bypass the BBB

in a passive manner, but instead potentially harnesses physiological cell trafficking pathways as a form of guided delivery.

Preclinical studies have provided early support for the feasibility of this concept. For example, albumin-based nanoparticles delivered through the cranial bone marrow route were reported to achieve substantial enrichment at brain lesion sites even at very low doses, suggesting that this pathway may offer high delivery efficiency when coupled to endogenous migratory mechanisms. Preliminary human observations have also suggested a basic safety profile for local skull bone marrow administration, further increasing interest in this strategy as a possible precision brain delivery route[184,185]. These findings are important because they suggest that skull–meninges-associated pathways could expand the current landscape of CNS drug delivery beyond conventional vascular, nasal, or meningeal lymphatic routes.

At the same time, this approach remains highly exploratory, and several important questions remain unresolved. The anatomical variability, transport kinetics, cell-type specificity, and ultimate parenchymal distribution of therapeutics delivered through these channels are not yet fully defined. It is also unclear to what extent this pathway can support repeated administration, broad regional drug distribution, or delivery of different cargo classes beyond selected nanoparticle systems[20]. Moreover, because this route relies at least in part on immune cell-mediated trafficking and lesion-related signaling, its performance may be strongly influenced by disease state, inflammatory context, and patient-specific biology[186]. Therefore, skull–meninges vascular or microchannel-associated delivery should currently be regarded as an emerging and conceptually innovative bypass strategy, with particular value in reshaping how brain delivery routes are understood rather than as an established translational platform for PD therapy.

6.4 Convection-enhanced delivery and local intracranial administration

Convection-enhanced delivery (CED) and related local intracranial administration strategies represent the most direct approach to bypassing the BBB. Unlike systemic or anatomical-route-based delivery methods, these techniques rely on stereotactic placement of infusion devices into target brain regions, allowing therapeutic agents to be introduced directly into the parenchyma or its immediate extracellular environment. In CED, continuous low-flow infusion generates a pressure gradient that drives bulk convective movement of the infused agent through the interstitial space, thereby enabling broader and more controlled distribution than would be achieved by passive diffusion alone[187]. This feature makes CED particularly attractive for PD therapies involving large molecules, viral vectors, neurotrophic factors, or other cargos that are poorly suited to systemic brain delivery[188].

In PD, the most prominent applications of CED have focused on neurotrophic factor-based neuroprotection and gene therapy. Neurotrophic factors such as GDNF have long been considered highly promising because of their capacity to support dopaminergic neuron survival and repair, yet their therapeutic translation has been constrained by delivery barriers and insufficient target-site exposure[189]. CED offers a potential solution by enabling high local concentrations within disease-relevant structures, such as the putamen or related basal ganglia regions. Similarly, gene therapy strategies have employed CED to deliver viral vectors carrying therapeutic genes directly into the brain, with the goal of achieving sustained local expression of beneficial proteins rather than repeated systemic administration[190].

Although CED can be performed with free drugs, nanocarriers provide distinct added value. Encapsulation of fragile biologics (eg, nucleic acids) in nanoparticles protects them from enzymatic degradation during infusion and prolongs their activity in the brain parenchyma[191]. Moreover, nanocarriers can be engineered to achieve sustained local release, thereby reducing the need for repeated infusions[192]. Optimized particle size and surface properties can also minimize backflow along the catheter tract, a common limitation of CED with free solutions[193]. For example, 1 study employed engineered polyethylene glycol-poly (β-amino ester) nanoparticles (PEG-PBAE NPs) carrying human GBA1 plasmid DNA to achieve localized, nonviral *GBA1* gene therapy via intracranial CED. In a mouse model of PD induced by α-synuclein PFFs, this strategy achieved efficient and sustained GBA1 transgene expression in the substantia nigra, significantly reduced α-synuclein aggregation, protected tyrosine hydroxylase-positive dopaminergic neurons, alleviated neuroinflammation, and improved motor function metrics such as grip strength, rod test, and open field performance. Compared with viral vectors, PEG-PBAE NPs offer the advantages of low immunogenicity, repeatable administration, and low cost, providing a potential strategy for shifting PD treatment from symptomatic management toward disease modification[194].

Furthermore, the practical performance of CED depends critically on how accurately the infused agent can be distributed within the brain tissue. A notable example is the use of AAV2-GDNF delivered by CED to the bilateral putamen in patients with PD. Although the infusion was stereotactically targeted to the intended structure, subsequent evaluation revealed that GDNF expression extended beyond the putamen into adjacent regions such as the caudate nucleus. This finding underscores a central issue in CED-based therapy: the actual intraparenchymal spread of therapeutic agents may not remain confined to the intended anatomical target, but may instead follow low-resistance pathways such as perivascular spaces or tissue interfaces[188]. Thus, while CED bypasses the BBB very effectively, it introduces a different challenge—namely, how to achieve predictable, regionally appropriate distribution within a heterogeneous brain environment.

This challenge is compounded by several additional factors that affect clinical translation. Drug distribution during CED can vary substantially because of interindividual anatomical differences, tissue anisotropy, local pressure gradients, catheter placement, and reflux along the catheter tract. Conventional single-port catheters may produce uneven distribution, incomplete target coverage, or backflow of infusate, particularly when delivering large biologics or viral particles. These limitations have motivated substantial interest in device innovation as a key determinant of CED success rather than a secondary technical detail[187,195].

Recent developments in catheter engineering illustrate how delivery hardware can reshape the feasibility of local intracranial administration. For example, multiporous perfusion catheters fabricated using precision laser drilling have been developed to improve the uniformity of intratissue convection and suppress reflux. By incorporating a permeable segment with multiple outlet pores, these devices are intended to distribute infusate more evenly and to better match the structural properties of brain tissue. Experimental studies have suggested that such catheters can deliver model therapeutics spanning a broad size range, from small molecules to viral-vector-scale particles, with high transmission efficiency and reduced clogging, while also improving intraparenchymal distribution during higher-flow infusions. These findings indicate that catheter design may be just as important as therapeutic cargo selection in determining the eventual success of CED-based therapy[196].

Overall, CED and local intracranial administration provide a uniquely powerful route for PD treatment because they can bypass the BBB most directly and support the delivery of cargos that are otherwise extremely difficult to administer to the brain. At the same time, their translational value depends not only on the biological efficacy of the infused therapy, but also on the precision, reproducibility, and safety of the infusion system itself. For this reason, the future of CED in PD will likely depend on

the integration of optimized therapeutic cargos with advanced catheter technology, real-time imaging guidance, and individualized treatment planning[197,198].

7. Comparative evaluation of crossing and bypass strategies

Crossing and bypass strategies represent 2 fundamentally different solutions to the same delivery problem in PD. BBB-crossing approaches attempt to negotiate directly with the endothelial barrier by exploiting endogenous transport pathways, enhancing transcytosis, or transiently increasing BBB permeability. Their major advantage is that they are generally compatible with systemic administration and may preserve broader access to deep brain regions without the need for direct intracranial intervention. However, their performance is often constrained by limited transport efficiency, endothelial retention, off-target uptake, and the difficulty of achieving quantitatively meaningful drug accumulation in the brain parenchyma[165,199]. By contrast, bypass strategies reduce reliance on classical transvascular BBB transport by exploiting alternative anatomical routes or local administration. These approaches may provide more direct brain access for selected cargos, but they typically introduce a different set of limitations, including restricted delivery flux, uneven regional distribution, procedural invasiveness, or route-specific variability[200]. As summarized in Table 1, the relative value of each strategy depends less on whether it is formally categorized as "crossing" or "bypassing" and more on its compatibility with cargo type, target region, dosing pattern, and acceptable procedural complexity.

From a therapeutic perspective, the relative value of these 2 strategy groups depends strongly on cargo type and treatment goal. BBB-crossing systems may be better suited to therapies that require repeated systemic administration or broad integration into existing pharmacological regimens, especially when the cargo can be effectively incorporated into ligand-modified or multifunctional nanoplatforms[50,204]. In contrast, bypass strategies may be particularly attractive for fragile macromolecules, high-local-dose therapies, or formulations that show extremely poor systemic brain exposure. For example, intranasal delivery offers a noninvasive and repeatable route, but its performance is limited by mucosal barriers and deposition efficiency[205]. Meningeal lymphatic-associated and skull–meninges-related routes expand the conceptual landscape of brain delivery, yet their transport dynamics and translational reproducibility remain less established[20,180]. Local intracranial approaches such as CED provide the most direct BBB bypass, but their success depends heavily on catheter design, distribution control, and procedural precision[206].

Overall, neither crossing nor bypass strategies should be viewed as universally superior. Instead, their utility should be judged according to the therapeutic cargo, the target brain region, the required dosing pattern, and the acceptable level of procedural complexity. In PD, where treatment needs range from chronic small-molecule management to biologics, gene therapy, and neurorestorative intervention, the most effective future approach is unlikely to be a single dominant route. Rather, progress will depend on developing cargo-matched and clinically realistic delivery strategies that balance access, precision, repeatability, and safety.

8. Translational challenges and future perspectives

Despite the remarkable preclinical performance of many multifunctional nanoplatforms described above, their translation into clinically viable therapies for PD faces substantial hurdles that are often insufficiently addressed in proof-of-concept studies. A critical gap exists between robust preclinical efficacy and clinical reality: although preclinical studies in PD models have demonstrated superior brain exposure, target engagement, and behavioral improvements compared with free drugs, the number of CNS-directed nanomedicine candidates that have advanced into human trials remains extremely limited. Several interconnected barriers collectively contribute to this translational bottleneck.

Manufacturing scalability, batch consistency, and long-term storage stability represent the primary foundational obstacles for clinical translation of nanomedicines. Most sophisticated nanoplatforms, particularly those incorporating biomimetic membranes, multiligand decorations, stimuli-responsive components, or complex drug combinations, are typically synthesized at the milligram scale using nonstandardized laboratory procedures that are often incompatible with large-scale Good Manufacturing Practice requirements. Scaling up production by several orders of magnitude to achieve the kilogram quantities required for animal safety testing and clinical trials frequently necessitates significant process changes, which can easily alter critical quality attributes such as particle size, surface charge, and drug loading capacity, leading to substantial batch-to-batch variability or even loss of core functionality. For biomimetic systems, the sourcing of membranes from cell cultures introduces additional variability in membrane composition and bioactivity, and source control and manufacturing standardization remain largely unresolved issues. These manufacturing challenges are not merely technical details; they fundamentally determine whether a nanoplatform can be produced consistently, cost-effectively, and in sufficient quantities to enter clinical evaluation. A realistic assessment must recognize that the structural complexity of nanoplatforms often inversely correlates with translational feasibility: while complex, multifunctional designs are valuable for exploring biological mechanisms and demonstrating proof of concept, the priority for clinical translation should be formulations that are mechanistically clear, technically robust, and practically scalable[207,208].

Rigorous quantification of successful delivery and target precision constitutes a core biological challenge constraining the translation of nanomedicine for PD. Many preclinical studies report only overall brain accumulation enhancement, improved behavioral outcomes, or reduced pathological burden, but the actual amount of therapeutic cargo reaching the relevant brain parenchyma (eg, the substantia nigra pars compacta and striatal projection regions), the specific cell populations exposed, and the duration of effective retention at target sites often remain poorly defined. For PD, therapeutic benefit depends not only on whether the drug enters the brain, but critically on whether it can be precisely delivered to key targets such as dopaminergic neurons in the substantia nigra pars compacta and their striatal projection areas. Currently, standardized and quantitatively robust frameworks for evaluating nanomedicine biodistribution, target engagement, and regional pharmacokinetics are largely absent[209]. This absence not only hampers crossstudy comparisons but also prevents the establishment of clear dose–response relationships between preclinical efficacy and actual delivered doses. Furthermore, inconsistency in the characterization and reporting of nanomaterial physicochemical properties further complicates quantitative delivery assessment and represents a major reason why preclinical outcomes are difficult to replicate in clinical trials[210].

Long-term safety and biocompatibility represent another major translational barrier for PD nanomedicines, particularly critical for chronic neurodegenerative diseases that require sustained or repeated dosing. A clinically valuable delivery system must not only be effective after a single administration but must also remain well-tolerated under long-term repeated use. This concern applies to both BBB-crossing and bypass strategies[211]. Different types of delivery systems carry distinct safety risks: ligand-modified or cationic nanoplatforms may increase off-target uptake in peripheral organs, trigger immunogenic

Table 1

Comparative evaluation of BBB-crossing and BBB-bypassing nanomedicine strategies for Parkinson disease.

Strategy	Typical cargos	Key strengths	Main limitations	Repeat dosing potential	Invasiveness
Carrier-mediated transport[201]	Selected small molecules; compact nanocarriers	Uses endogenous nutrient transport pathways; compatible with systemic delivery	Limited capacity; substrate competition; less suitable for large or complex cargos	Moderate to high	Low
Receptor-mediated transport[85]	Proteins, antibodies, nucleic acids, multifunctional nanoplatforms	Strong BBB-targeting rationale; adaptable ligand design; suitable for complex cargos	Endothelial retention; off-target uptake; receptor heterogeneity	Moderate to high	Low
Adsorptive-mediated transcytosis[202]	Cationic nanocarriers; selected macromolecules	Does not rely on a single receptor; broadly applicable design principle	Nonspecific binding; lower selectivity; toxicity risk	Moderate	Low
Biomimetic delivery[43]	RNA drugs, proteins, sensitive multifunctional cargos	Improved circulation, immune evasion, and biointerface compatibility	High complexity; unclear mechanisms; poor standardization	Moderate	Low
Focused ultrasound-assisted BBB opening[131]	Biologics, neurotrophic factors, enzymes, gene vectors, nanoparticles	Region-specific and noninvasive BBB opening; enables poorly penetrant cargos	Parameter-sensitive; safety and reproducibility require tight control	Moderate	Low to moderate
Photothermal BBB modulation[9]	Small molecules, nucleic acids, multifunctional nanosystems	Integrates BBB modulation with stimulus-responsive release	Limited light penetration; thermal safety concerns; low clinical maturity	Low to moderate	Low
Intranasal delivery[154]	Small molecules, peptides/proteins, some nucleic acids	Noninvasive and repeatable; reduces systemic exposure	Limited flux; variable deposition; mucosal barriers	High	Low
Meningeal lymphatic-associated pathways[175]	Nanoparticles; immunomodulatory systems; selected drugs/biologics	Bypasses classical BBB; may link delivery with clearance and immune modulation	Transport dynamics and efficiency remain incompletely defined	Moderate	Low to moderate
Skull–meninges microchannel-associated pathways[203]	Selected nanoparticles; cell-associated systems	Conceptually novel; potential lesion-oriented delivery	Highly exploratory; unclear kinetics and generalizability	Unknown to low	Moderate
CED/local intracranial administration[187]	Large biologics, viral vectors, neurotrophic factors	Most direct BBB bypass; high local exposure	Invasive; distribution variability; catheter dependence	Low to moderate	High

responses, or induce cerebrovascular endothelial stress[212]; physical BBB-opening methods such as FUS and photothermal modulation must carefully balance delivery efficiency against the risk of neurovascular injury[213]; and local intracranial administration routes remain constrained by procedural invasiveness and the potential risks associated with uneven drug distribution[214]. Notably, most current preclinical safety studies only assess acute toxicity following single administration and are conducted in young, healthy animals, whereas PD patients are typically elderly with preexisting vascular dysfunction and neuroinflammation, factors that significantly alter BBB behavior and tissue responses to nanomaterials. This underscores the critical importance of long-term safety evaluation in disease-relevant animal models. For nonbiodegradable inorganic nanomaterials, cationic carriers, and membrane-coated systems, the cumulative toxicity, long-term tissue retention, and potential chronic neuroinflammatory risks following repeated administration require more systematic characterization[215].

Regulatory uncertainty and clinical design complexity further complicate the translation of PD nanomedicines. Currently, global regulatory agencies lack harmonized guidelines specifically tailored to complex nanomedicines, making it difficult for developers to clearly navigate the development pathway and regulatory requirements. The significant heterogeneity in BBB permeability across PD patients, across different brain regions, and across disease stages complicates patient stratification, dosing regimen design, and endpoint selection in clinical trials. Moreover, demonstrating therapeutic benefit requires not only evidence of successful brain delivery but also confirmation of target engagement and clinically meaningful functional improvement, endpoints that are often difficult to measure reliably in small early phase trials. The poor reproducibility of preclinical outcomes in clinical trials, partly attributable to nonstandardized characterization and reporting of nanomaterial physicochemical properties and biological effects, has been recognized as a major contributor to translational failure[216,217].

Looking forward, the next stage of development in PD nanomedicine should move toward cargo-matched, disease-stage-aware, and clinically realistic delivery design. No single delivery route is likely to suit all therapeutic scenarios. Instead, small molecules, biologics, nucleic acids, and gene-based therapies may each require different combinations of carrier design, delivery route, and treatment schedule. At the same time, greater emphasis should be placed on image-guided delivery, real-time monitoring, patient stratification, and integration with precision devices or minimally invasive administration technologies. Ultimately, the most impactful future strategies will likely be those that balance therapeutic performance with practical scalability, safety, and regulatory tractability—approaches that achieve reliable brain delivery while remaining compatible with the real-world demands of PD treatment.

9. Conclusions

PD remains constrained not only by the limited availability of disease-modifying therapies, but also by the persistent difficulty of achieving effective brain delivery. In this context, nanomedicine offers a versatile platform for improving the therapeutic potential of both conventional drugs and emerging biologics. Current strategies broadly fall into 2 categories: those designed to cross the BBB and those intended to bypass it, each with distinct advantages and limitations. Rather than identifying a universally optimal route, future progress in PD treatment will depend on matching delivery strategies to specific cargos, target regions, and clinical scenarios. Ultimately, the success of nanomedicine in PD will rely on achieving a practical balance between delivery efficiency, safety, manufacturability, and translational feasibility.

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Conflicts of interests

The authors declare that they have no conflicts of interest.

Author contributions

Xiao Xiao, Keyang Xu, and Kexin Ni contributed equally to this work. They conceived and organized the review, performed the literature search, and wrote the original draft. Yongzhen Su, Yadan Shi, Mengyao Wu, Xiuqi Hu, and Jianxian Ge contributed to visualization, data curation, and manuscript revision. Jianfeng Zeng supervised the project, acquired funding, and reviewed and edited the manuscript. All authors discussed and approved the final manuscript.

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