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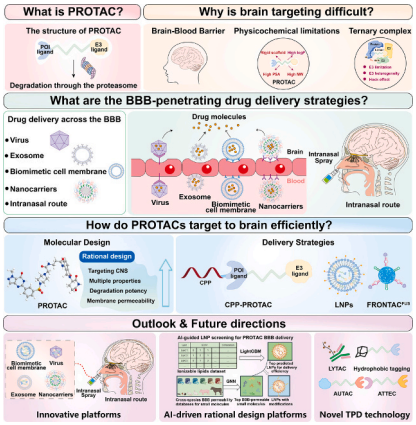
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Engineering brain-penetrant PROTACs: Bridging molecular design and CNS delivery☆,☆☆

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GRAPHICAL ABSTRACT



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ABSTRACT

The drug development for central nervous system (CNS) disorders, particularly neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease, faces formidable challenges. While

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Delivery platforms
Molecular design
Blood-brain barrier
Neurodegenerative diseases

proteolysis-targeting chimeras (PROTACs) represent a paradigm-shifting modality by redefining target engagement mechanisms, their clinical translation remains hindered by limited blood-brain barrier (BBB) permeability and suboptimal pharmacokinetic profiles. In recent years, a range of CNS-targeted delivery strategies have emerged, advancing PROTAC research toward more translatable therapeutic applications. This review highlights recent advances and persistent challenges in noninvasive BBB-penetrant delivery systems, including viral vectors, engineered exosomes, functionalized nanocarriers, and cell membrane-derived biomimetic vehicles, with a particular emphasis on intranasal administration as a direct route to the brain. Parallel progress in rational molecular engineering, encompassing E3 ligase selection, linker polarity and rigidity modulation, and optimization of target-binding ligands, has further enhanced PROTAC drug-likeness and BBB transport efficiency. Current CNS-directed PROTAC designs increasingly incorporate cell-penetrating peptides, nanoparticles, and prodrug formulations to balance stability, selectivity, and brain exposure. Future advanced PROTAC delivery platforms require integrating multifunctional nanocarriers with rational structural optimization to enhance BBB permeability. Further artificial intelligence-accelerated molecular design and targeted protein degradation technologies offer novel avenues for addressing undruggable CNS targets.

1. Introduction

Neurodegenerative diseases (NDs) represent a heterogeneous group of disorders characterized by progressive neuronal loss and functional deterioration, manifesting clinically as cognitive decline and/or motor dysfunction. Major NDs, including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), share a convergent molecular pathology centered on proteostasis failure, the misfolding, aggregation, and insufficient clearance of specific pathogenic proteins such as Aβ and tau in AD, α-synuclein in PD, and mutant huntingtin (mHTT) [1]. The progressive accumulation of these toxic protein species disrupts synaptic integrity, mitochondrial function, and neuronal signaling, ultimately driving irreversible neurodegeneration [2–4]. Despite extensive efforts, therapeutic progress has been hindered by the intrinsic "undruggable" nature of these pathogenic proteins. They often lack well-defined ligandable pockets, participate in complex protein-protein interaction networks, and exhibit conformational heterogeneity, all of which render classical small-molecule inhibition largely ineffective. Taken together, these repeated failures to pharmacologically modulate pathogenic proteins highlight a fundamental limitation of conventional "occupancy-driven" pharmacology in restoring neuronal proteostasis.

Against this backdrop, proteolysis-targeting chimeras (PROTACs) have emerged as a transformative modality that redefines the drug-target paradigm. By hijacking the endogenous ubiquitin-proteasome system (UPS), PROTACs recruit disease-relevant proteins to E3 ubiquitin ligases, enabling selective and catalytic degradation rather than transient inhibition [5] (Fig. 1). This "event-driven" mechanism offers several advantages over conventional occupancy-based small molecules and other therapeutic approaches. A key advantage is that by degrading rather than merely inhibiting target proteins, PROTACs can access the vast "undruggable" proteome, including scaffolding proteins, transcription factors, and aggregation-prone species that lack enzymatic active sites or well-defined binding pockets [6]. Second, because PROTACs can act substoichiometrically and are functionally recycled after inducing ubiquitination, they may enable sustained target suppression with distinct exposure-response characteristics relative to occupancy-based agents [7]. This potentially improve patient compliance in chronic neurodegenerative conditions. In addition, by removing the protein rather than blocking a single active site, PROTACs may mitigate certain resistance liabilities associated with target overexpression or adaptive pathway reactivation. Fourth, PROTACs offer the potential for enhanced selectivity through the requirement of ternary complex formation, which can exploit subtle differences in protein surface topology. Finally, these mechanistic attributes make PROTACs particularly attractive for NDs, where selective degradation of misfolded or aggregation-prone proteins could directly restore proteostatic balance in neurons [8]. Nevertheless, the translation of PROTACs into

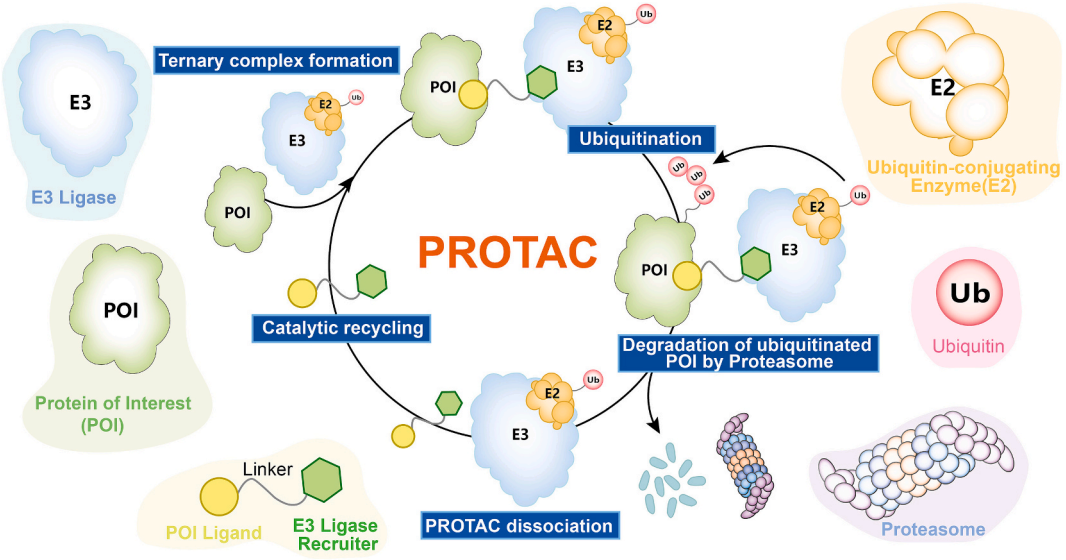


Fig. 1. Schematic of PROTAC mechanism. The PROTAC molecule comprises three components: a targeting ligand for the protein of interest (POI), an E3 ubiquitin ligase-binding ligand, and a bifunctional linker. By inducing proximity between the POI and E3 ligase, the PROTAC enables E2-mediated ubiquitin transfer to the POI. Polyubiquitinated POI is subsequently recognized and degraded by the 26S proteasome. The reusable PROTAC molecule dissociates upon degradation to initiate subsequent catalytic cycles.

neurotherapeutics is far from straightforward, as challenges such as limited blood-brain barrier (BBB) permeability, target engagement within the central nervous system (CNS), and off-target toxicity remain formidable. Addressing these barriers requires integrated advances in molecular design and delivery strategies, areas that are now emerging as the focal points of next-generation PROTACs research for neurodegenerative diseases.

Although the PROTAC paradigm holds transformative potential for targeting pathogenic proteins in neurodegenerative diseases, translating PROTACs to CNS indications remains challenging, largely because achieving sufficient brain exposure and intracellular availability is difficult. Many PROTACs occupy beyond-rule-of-five physicochemical space, often characterized by high molecular weight and polarity, which limits passive CNS penetration and can increase susceptibility to transporter-mediated efflux, thereby constraining intracerebral exposure [9]. Beyond BBB permeability, successful CNS application requires navigating additional hurdles including metabolic stability, intracellular delivery, and target engagement within the complex brain microenvironment, while maintaining adequate stability, selectivity, and safety. Thus, these considerations indicate that the key challenge is not merely one of BBB transport, but of achieving coherent integration between degradation efficiency and brain accessibility.

To surmount this physiological bottleneck, a growing body of research converges on the synergistic integration of molecular design and delivery engineering, representing the most promising path toward brain-accessible PROTACs. At the molecular scale, rational structural optimization focuses on fine-tuning linker topology, physicochemical attributes, and E3-target ligand composition to reconcile two intrinsically conflicting demands, retaining high degradation efficiency while minimizing molecular size, polarity, and efflux susceptibility. In parallel, advanced delivery systems , including nanocarriers, exosomes, and non-invasive administration routes, offer complementary strategies to escort PROTACs across biological interfaces and enhance target-site precision [10–16]. Collectively, these advances delineate a multi-scale design paradigm, in which molecular re-engineering and delivery innovation coalesce to redefine the boundaries of CNS druggability. Rather than existing as separate disciplines, chemistry, pharmacology, and delivery science are converging into an integrative framework of "design-deliver-degrade", signaling a conceptual shift from incremental formulation improvement toward the systemic orchestration of pharmacokinetic and pharmacodynamic control. This evolution marks not merely a technical frontier but the emergence of a unified strategy for achieving precise, brain-targeted proteolysis.

In summary, realizing the therapeutic potential of PROTACs in neurodegenerative diseases will require a conceptual and technological synthesis that extends beyond conventional drug discovery. While rational molecular design and advanced delivery systems collectively provide the structural and pharmacological foundation for brain-accessible degraders, the next leap will depend on integrating these principles within a systems-level framework. In this context, multi-scale modeling, AI-guided optimization, and quantitative BBB transport analytics may enable predictive control over degrader distribution, target engagement, and proteostatic outcomes [17–19]. This Review delineates the current state and future trajectory of brain-targeted PROTAC research, providing a mechanistic foundation for next-generation therapeutic development. Ultimately, the convergence of chemistry, pharmacology, and delivery science is redefining the boundaries of CNS druggability and offering a transferable blueprint for precise modulation of intracellular protein homeostasis. Such integration is poised to transform neurodegenerative disease therapy, from symptomatic intervention toward durable, mechanism-driven restoration of neuronal function.

2. Multiscale barriers and core challenges in brain delivery of PROTACs

Despite their promise as a transformative therapeutic modality for neurodegenerative diseases, PROTACs face formidable translational barriers, with more than 70% of candidate molecules failing to achieve clinical viability [20–26]. For CNS indications, the central challenge is not a single gate but a multiscale delivery problem spanning-transport across the BBB, systemic exposure and metabolic stability, cellular and subcellular access to enable productive degradation. While BBB penetration is often viewed as the dominant hurdle [27–29], brain exposure alone is insufficient: PROTACs must reach the cytosol of relevant neural cell types at adequate free concentrations, evade efflux and nonspecific binding, and overcome endocytic sequestration and limited endosomal escape. These challenges are rooted in a fundamental physicochemical paradox: the very structural complexity that endows PROTACs with catalytic degradative power simultaneously impedes their permeability and bioavailability within the central nervous system [30]. Ultimately, their pharmacological efficacy depends not merely on brain penetration but on efficient ternary complex formation at substoichiometric concentrations within the neural milieu, a process that is further constrained by the biochemical and biophysical characteristics of the brain environment [31–33].

This section systematically dissects the multiscale barriers that collectively limit PROTAC delivery to the brain, encompassing molecular-level constraints intrinsic to PROTAC architecture, the multilayered defense mechanisms of the BBB, and the dynamic influences of the cerebral microenvironment and disease state (Fig. 2). By examining these interconnected challenges, it aims to illuminate the mechanistic foundations underlying the translational bottleneck of PROTACs in neurodegenerative therapeutics and provide a conceptual framework for rational design and delivery optimization.

2.1. Physicochemical constraints undermining the brain accessibility of PROTACs

The brain delivery of PROTACs faces formidable challenges, primarily arising from their intrinsic molecular architecture. The physicochemical properties of PROTACs differ markedly from those of traditional CNS drugs [34–37]. Whereas small molecules with good BBB permeability typically conform to Lipinski's rule of five, PROTACs almost invariably violate these parameters [38–41]. As heterobifunctional molecules comprising a target ligand, an E3 ubiquitin ligase ligand, and a linker, they possess inherently high molecular weights and large polar surface areas (PSA) [42,43]. Such features drastically reduce their capacity for passive diffusion across the BBB, representing a principal cause of their limited brain exposure [44,45].

In addition, their rigid structures and abundance of hydrogen bond donors and acceptors further restrict passive diffusion through the lipid bilayer, the predominant route of CNS entry for conventional drugs [43,46]. Many PROTACs also display high logP values, predisposing them to strong, non-specific binding with biomembranes or plasma proteins [47,48]. This reduces the free-drug fraction, diminishes effective brain accumulation, and may accelerate metabolic clearance.

Importantly, the challenge for PROTACs extends beyond BBB traversal [49,50]. Even upon reaching the brain parenchyma, these large, polar molecules must still penetrate cellular membranes to access the cytosol, where they execute degradation of the target protein. For most PROTACs, the upper limit of pharmacological efficacy is ultimately determined by their effective free exposure within target cells (neurons, astrocytes, and microglia) and their ability, once inside cells, to form a productive ternary complex and trigger ubiquitin-proteasome-mediated degradation. Growing evidence suggests that cellular uptake of many PROTACs is not governed by simple passive diffusion but is closely associated with receptor-mediated endocytosis [51]. However, endocytic entry also introduces a characteristic risk of endosomal

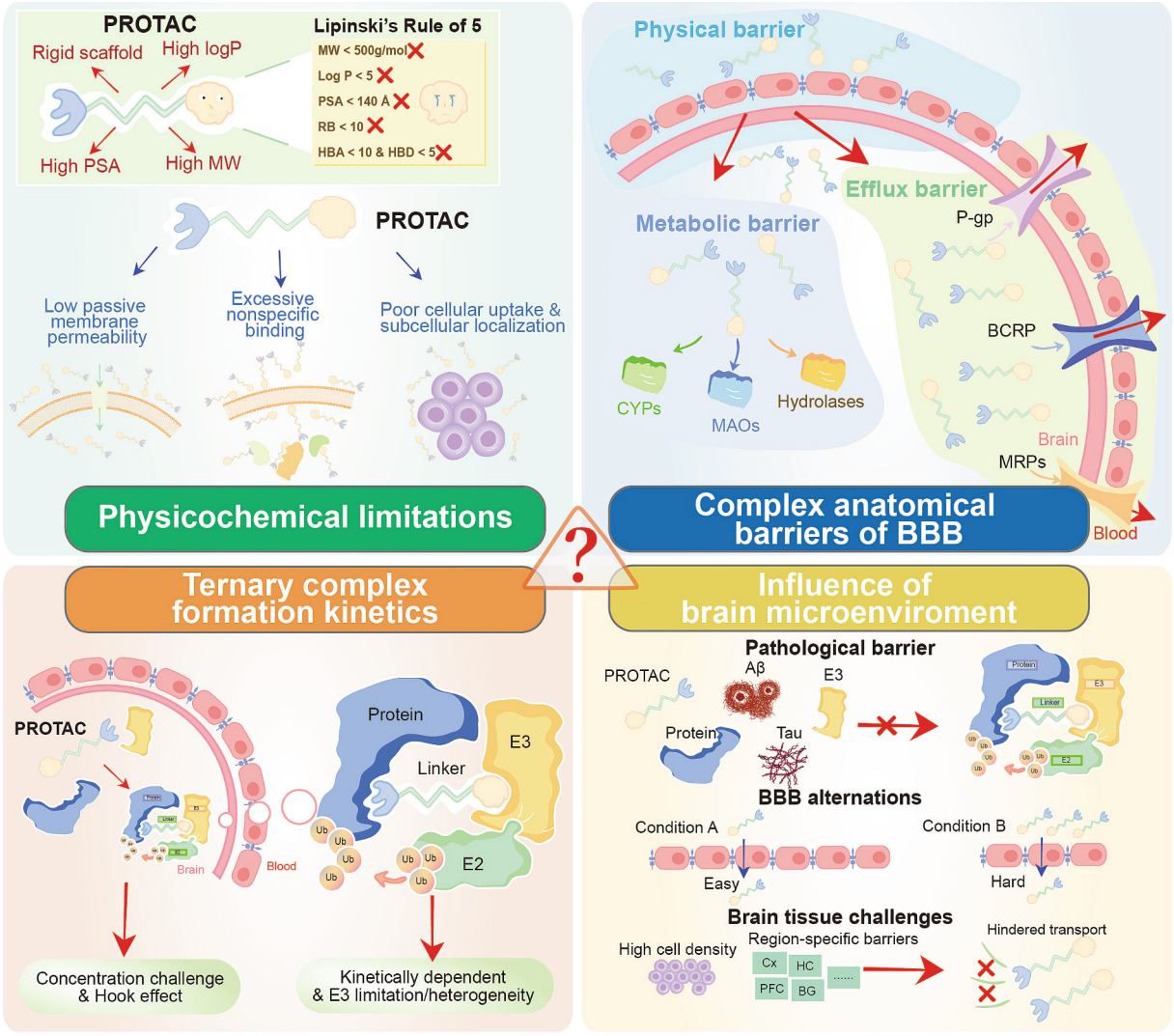


Fig. 2. Multiscale barriers and core challenges in brain delivery of PROTACs. The inherent physicochemical properties of PROTACs, including high molecular weights, large polar surface areas (PSA), and high logP values, and the multifaceted physiological barriers of BBB severely restrict efficient PROTAC brain delivery. The Hook effect and E3 ligases tissue-specific expression restrain target protein degradation efficiency in the brain. The brain's unique microenvironment and pathological conditions further reshape dynamic tissue distribution of PROTACs.

sequestration. Even if PROTACs successfully traverse the BBB and enter the brain parenchyma via receptor-mediated uptake or related mechanisms, they are often enclosed within intracellular vesicles (such as endosomes) rather than reaching their site of action [52]. In the absence of efficient endosomal escape, these PROTACs may face two fates: degradation by acidic hydrolytic enzymes as endosomes mature into lysosomes, or re-export to the extracellular space via efflux processes [53,54]. Therefore, achieving transport across the BBB alone is insufficient to ensure efficacy. Systemically enhancing cellular uptake, promoting endosomal escape, and achieving cell-type selectivity to enable the cytosolic accumulation of PROTACs represent another decisive step for successful target protein degradation.

Collectively, the various inherent, suboptimal physicochemical properties of PROTACs severely restrict their efficient intracellular delivery and localization, thereby rendering the entire drug delivery pathway within the CNS particularly complex and arduous. This limitation not only exemplifies the conflict between molecular complexity and CNS drug-likeness, but also underscores the need to rethink the physicochemical paradigms that define "druggability" in the brain. Bridging this gap will require an integrated strategy that couples rational molecular re-engineering with advanced delivery approaches.

2.2. The multifaceted physiological barriers of the BBB impeding PROTAC brain delivery

The BBB is primarily formed by brain capillary endothelial cells interconnected through tight junction proteins, which almost completely seal the paracellular pathways [28]. This forces most molecules to employ a transcellular route for BBB traversal [55]. This intricate tight junction network, together with pericytes and astrocytic end-feet, constitutes a robust physical barrier. Consequently, large and polar molecules such as PROTACs face pronounced difficulty penetrating the BBB through passive diffusion and must rely on specific transport mechanisms, thereby imposing stringent constraints on their molecular design.

Beyond this structural barrier, BBB endothelial cells express an extensive repertoire of efflux transporters, including P-gp, Breast Cancer Resistance Protein (BCRP), and Multidrug Resistance-Associated Proteins (MRPs) [56–58]. These transporters actively recognize and expel xenobiotics that enter endothelial cells, thereby creating a dynamic regulatory interface that further restricts brain entry. Notably, several PROTACs have been identified as substrates of these efflux systems, particularly when their hydrophobic domains facilitate transporter recognition [59,60]. This active efflux severely limits intracerebral

accumulation, such that even molecules that transiently cross the BBB may be rapidly cleared back into the circulation.

In addition to efflux, the BBB functions as a metabolic barrier enriched in enzymes such as cytochrome P450 isoforms, monoamine oxidases, and hydrolases [61]. These enzymes can rapidly metabolize PROTACs in circulation, leading to accelerated clearance and shortened systemic half-life, thereby compounding the difficulty of achieving effective brain bioavailability [62]. Together, these physical, transport, and metabolic defenses represent a multifaceted physiological checkpoint that maintains CNS homeostasis but simultaneously poses a formidable challenge to the successful delivery of large, complex modalities such as PROTACs.

2.3. Ternary complex dynamics and E3 ligase biology in brain-targeted PROTACs

2.3.1. Dynamics of ternary complex formation

The hallmark of PROTAC technology lies in its catalytic mechanism, which induces the formation of a ternary complex between the target protein and an E3 ubiquitin ligase, thereby triggering ubiquitination and subsequent proteasomal degradation. However, this event-driven mechanism is not merely a binding process but a finely balanced thermodynamic and kinetic system whose efficiency determines both degradation potency and selectivity [63]. The assembly of the ternary complex requires not only favorable binary affinities between the PROTAC and its two binding partners but also positive cooperativity that stabilizes the composite interface [64]. Achieving this balance is inherently difficult, as excessive binary affinity may suppress cooperative assembly, whereas insufficient affinity yields transient or unstable complexes.

From a structural perspective, the geometry and flexibility of the linker critically shape the spatial orientation of the target-E3 pair, influencing both the entropic cost of complex formation and the kinetics of ubiquitin transfer [65]. These parameters become even more restrictive within the brain microenvironment, where lower drug concentrations, higher macromolecular crowding, and altered redox or ionic conditions may further destabilize transient multiprotein assemblies. Thus, optimizing ternary complex formation for CNS applications requires a nuanced understanding of the dynamic interplay among affinity, cooperativity, and conformational adaptability, factors that together define the catalytic landscape of PROTACs in the nervous system.

Furthermore, in the context of the brain, the efficiency of ternary complex formation becomes a kinetic bottleneck constrained by limited molecular exposure. Only a minute fraction of systemically administered PROTACs can traverse the BBB and distribute within the parenchyma, resulting in substoichiometric concentrations at the site of action [66]. Under these conditions, productive ternary assembly competes unfavorably with diffusion, degradation, and non-productive interactions, rendering the overall degradation process highly dependent on catalytic turnover efficiency. Achieving meaningful pharmacological activity within this narrow exposure window, therefore, requires PROTACs that exhibit exceptionally high catalytic proficiency, rapid complex formation kinetics, and prolonged residence in the brain microenvironment.

However, the absence of quantitative pharmacokinetic and spatial distribution data for most PROTACs prevents accurate prediction of their catalytic behavior within the CNS [67,68]. The interplay between local concentration, ternary-complex cooperativity, and degradation kinetics remains poorly defined, leading to substantial uncertainty in clinical translation. Moreover, attempts to compensate for poor brain penetration by increasing systemic dose can paradoxically impair degradation efficiency through the hook effect, a non-linear kinetic phenomenon in which excessive PROTAC molecules saturate either the target or the E3 ligase, favoring non-productive binary complexes over the desired ternary assembly [69]. This not only flattens the dose-response relationship but also increases systemic exposure and potential off-target degradation, thereby narrowing the therapeutic window. Collectively, these pharmacokinetic and kinetic constraints highlight the need for an integrated understanding of exposure-efficacy relationships specific to the CNS. Rational design of brain-targeted PROTACs will thus require predictive modeling that couples molecular cooperativity with brain pharmacodynamics, enabling optimization of degradation efficiency under physiologically relevant concentration regimes.

2.3.2. The E3 ligase landscape

Beyond kinetic and pharmacokinetic considerations, the biological landscape of E3 ligases imposes an additional layer of complexity on PROTAC-mediated degradation in the brain. The efficiency and selectivity of degradation are inherently contingent on the abundance, localization, and catalytic competence of the recruited E3 ligase. Yet, current PROTAC development relies predominantly on a narrow subset of well-characterized ligases-such as CRBN, VHL, IAPs, and MDM2, whose expression in the human brain is heterogeneous and, in many regions, exceedingly low [70–74]. This spatial and cell-type variability constrains the formation of productive ternary complexes across distinct neuronal populations, thereby limiting both potency and tissue specificity.

Recent proteomic and transcriptomic analyses have revealed a much broader, yet largely untapped, repertoire of brain-enriched E3 ligases, including FBXO41, FBXL16, TRAF3, and TRIM2, many of which display regional or cell-type-restricted expression patterns aligned with neuroanatomical function [71,75–80]. These ligases present dual implications: they offer unprecedented opportunities for designing brain-selective degraders, but they also underscore the challenge of achieving consistent efficacy across heterogeneous neural circuits (Table 1). Moreover, several E3 ligases such as MDM2 or IAPs play pleiotropic roles in cell cycle regulation, DNA repair, and stress responses [70,81,82]. Their dysregulation in neurodegenerative conditions introduces additional uncertainty, as recruiting such ligases may inadvertently perturb essential cellular pathways or exacerbate pathological cascades. Another underappreciated limitation arises from the tissue distribution and adaptive plasticity of E3 ligases. When the recruited ligase is highly expressed in peripheral tissues, PROTACs risk off-target degradation and systemic toxicity. Conversely, the downregulation or mutation of the E3 ligase under chronic treatment may drive pharmacological resistance, a phenomenon already observed in oncology models [83].

Collectively, these insights reveal that E3 ligase biology functions as both an enabler and a constraint for brain-targeted PROTACs. Comprehensive profiling of E3 expression and activity within the CNS, combined with rational or AI-guided ligase selection and engineering, will be indispensable for the next generation of neurodegenerative disease degraders. By integrating kinetic precision with tissue-specific ligase recruitment, future PROTACs may transcend current limitations and achieve the spatial and functional selectivity required for safe, effective, and durable modulation of neuronal proteostasis.

Table 1
E3 Ligases in Major Central Nervous System Cell Types.

CNS Cell Type	Major/Enriched E3 Ligases	Representative Reference
Neurons	UBE3A, FBXO41, RNF19A, RNF216	[75,84–86]
Astrocytes	NEDD4L, TRIM21, c-Cbl	[87–89]
Microglia/CNS macrophages	Peli1, c-Cbl	[89,90]
Oligodendrocytes/neuron-glia interface	TRIM family	[91]
Broad CNS E3 families	Cullin-RING ligases (e.g., CUL3, CUL4)	[92]

2.4. Dynamic modulation of PROTAC pharmacology by the brain microenvironment and disease remodeling

The pharmacological behavior of PROTACs within the central nervous system is profoundly shaped by the unique biophysical and pathological milieu of the brain. Beyond the formidable barrier of the BBB, the brain's intricate microarchitecture and dynamic tissue environment impose additional constraints on distribution, diffusion, and target engagement. The high cellular density, regional heterogeneity, and tightly organized extracellular matrix collectively limit the free diffusion of macromolecules, leading to pronounced spatial gradients in drug exposure [93]. These structural barriers are further compounded by the compositional diversity of different brain regions—each characterized by distinct neuron, glia ratios, lipid content, and vascular density, that can alter both the kinetics and local efficacy of PROTACs [94].

In neurodegenerative diseases such as AD and PD, pathological protein aggregates, including Aβ plaques, tau tangles, and Lewy bodies, further reshape the extracellular landscape, physically obstructing PROTAC access to intracellular targets and perturbing local proteostasis [95–107]. Moreover, neuroinflammatory responses accompanying these disorders can modify vascular permeability, pH, and redox balance, influencing both the stability and distribution of degraders [108,109]. The blood-brain barrier itself is not static but undergoes context-dependent remodeling during disease progression [110]. This remodeling can manifest as either increased permeability, as seen in glioblastoma, where the blood-brain tumor barrier (BBTB) exhibits partial disruption and selective leakiness, or as hyperstabilization, as reported in the early stages of AD, where tight junction reinforcement further restricts molecular entry [111]. Such bidirectional alterations introduce an additional layer of unpredictability, where disease stage and regional pathology jointly dictate the pharmacokinetic landscape of PROTACs.

Collectively, these microenvironmental and pathological variables transform the brain from a uniform pharmacological compartment into a highly heterogeneous and evolving system. Understanding how these factors dynamically modulate diffusion, metabolism, and target accessibility is essential for rational PROTAC design and delivery optimization. Overcoming these intertwined barriers will require the integration of multiscale modeling, disease-stage-specific pharmacokinetics, and adaptive delivery platforms capable of responding to local physiological cues. Only through such a systems-level understanding can the therapeutic potential of PROTACs in neurodegenerative and other CNS disorders be fully realized.

2.5. Structural complexity and its implications for brain delivery of PROTACs

A fundamental yet often underappreciated barrier to effective brain delivery of PROTACs arises from their inherent structural complexity and conformational dynamics. Unlike classical small molecules that typically exhibit rigid and predictable geometries, PROTACs form ternary complexes through transient and multivalent interactions between the target protein and an E3 ubiquitin ligase [112]. These interactions are not pre-existing but are induced and stabilized by the PROTAC molecule itself. Consequently, the conformational ensemble of PROTAC-mediated complexes is highly dynamic and context dependent, shaped by factors such as linker flexibility, solvent polarity, and cellular microenvironment. This dynamic nature complicates both experimental characterization and computational modeling, posing a major obstacle to rational design and delivery optimization.

Recent advances in structural biology, including cryo-electron microscopy and integrative computational approaches, have begun to elucidate the architectures of selected PROTAC-E3-target assemblies. However, most available structures capture only static conformations under cryogenic or artificial conditions that may not accurately reflect the dynamic equilibria in vivo. Cryo-EM, although powerful for large complexes, struggles to resolve the weak and transient interactions between PROTACs and their binding partners, often resulting in low-resolution or ambiguous density maps [33,113–116]. Similarly, while AlphaFold3 has revolutionized protein structure prediction, it remains limited in modeling induced-fit or ligand-bridged complexes such as those mediated by PROTACs, where the two proteins have minimal intrinsic affinity in the absence of the degrader. The lack of an evolutionary co-variation signal further restricts predictive accuracy [117,118].

This structural uncertainty has direct implications for drug delivery and pharmacodynamics within the central nervous system. The stability, orientation, and lifetime of the ternary complex determine not only degradation efficiency but also the effective intracellular concentration required to achieve catalytic turnover. Subtle variations in conformational plasticity or linker geometry can dramatically alter target engagement kinetics, cellular permeability, and even efflux susceptibility. For CNS applications, where available PROTAC concentrations are already constrained by the blood-brain barrier and systemic clearance, such structure-dependent variability may amplify pharmacokinetic inefficiencies. A deeper understanding of the dynamic structural landscape is therefore essential for bridging molecular design and delivery optimization (Fig. 3).

Emerging multidisciplinary approaches that integrate cryo-EM snapshots, molecular dynamics simulations, and machine-learning-based modeling are beginning to reveal the transient conformations that govern ternary assembly and dissociation [33,114,119]. These insights can inform rational linker design, modulate physicochemical parameters to favor brain penetration, and guide the development of conformationally adaptable scaffolds compatible with CNS delivery. Ultimately, resolving the structural dynamics of PROTACs is not merely a question of molecular visualization but a prerequisite for transforming them into viable therapeutics capable of maintaining stability, selectivity, and catalytic efficiency within the brain microenvironment.

In summary, the multiscale barriers encountered in CNS therapy impose major constraints on the stepwise delivery cascade of PROTACs. Elucidating how these barriers interact synergistically not only clarifies the fundamental translational bottlenecks limiting CNS-targeted PROTAC development, but also provides a theoretical foundation for the rational design of optimization strategies. Nevertheless, recognizing the obstacles alone is insufficient to overcome them. To truly breach these barriers and achieve efficient delivery of PROTACs to the brain, advanced carrier-based delivery technologies are urgently needed. Accordingly, building on the mechanistic framework outlined above, the next section will systematically summarize recently developed noninvasive brain-delivery platforms. These systems are designed not only to facilitate brain entry, but also to enhance cellular uptake and intracellular trafficking, thereby improving the intracellular availability required for PROTAC-induced protein degradation and opening new avenues for the application of PROTACs in CNS disorders.

3. Advances in drug delivery across the BBB

The development of effective drug delivery systems to the brain is fundamentally constrained by the complex anatomical and physiological properties of BBB [120]. Achieving efficient BBB penetration of therapeutics into neural cells constitutes a critical determinant for successful CNS-targeted therapeutics [121]. Despite enabling CNS drug delivery via invasive methods, including intracerebroventricular (ICV) application, intrathecal lumbar (IT-L) injections, and convection-enhanced delivery (CED), these approaches provoke neuroinflammatory responses and lack suitability for chronic neurodegenerative disorders like AD and PD, requiring sustained pharmacotherapy [122–126]. The development of non-invasive delivery platforms capable of targeting the brain constitutes a critical imperative for advancing next-generation CNS disease therapeutics. Recent advances in BBB biology have catalyzed the development of innovative CNS-targeted delivery platforms for therapeutic and diagnostic agents [127,128].

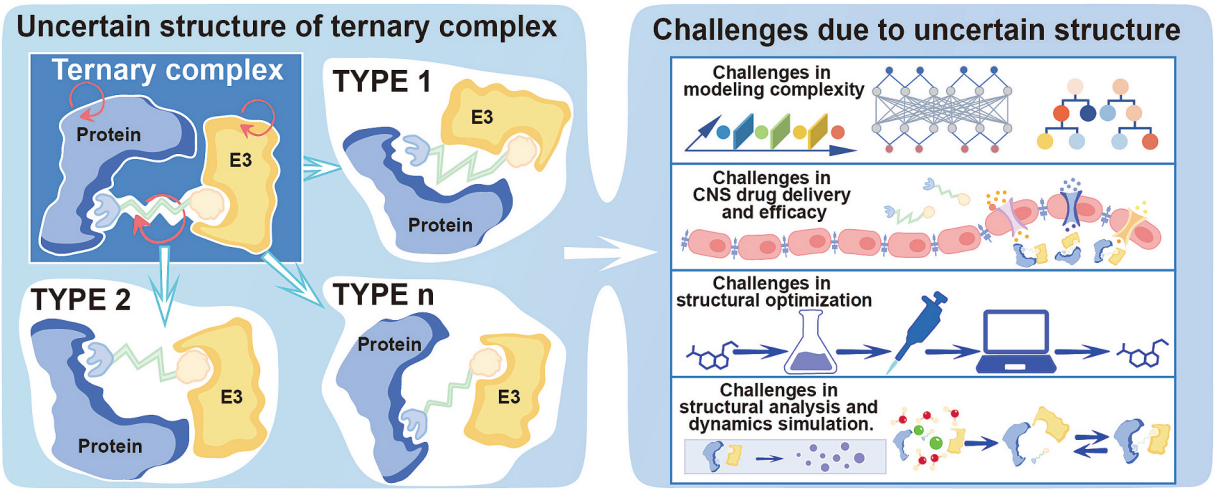


Fig. 3. Structural complexity and its implications for brain delivery of PROTACs. Owing to the conformational lability of the ternary complex, its intricate binding modes are difficult to resolve by cryo-electron microscopy and related methods. Reliable models for computational chemistry are lacking, hindering structure–activity relationship–driven optimization of PROTAC scaffolds to improve blood–brain barrier permeability.

However, most of these platforms were originally developed for small molecules, peptides, or nucleic acid therapeutics, and adapting them to PROTACs as a distinct therapeutic modality requires careful evaluation of their compatibility and limitations. This section details non-invasive brain delivery platforms, including viral vectors, exosomes, nanocarriers, cell membrane-based biomimetic systems, and subcellular

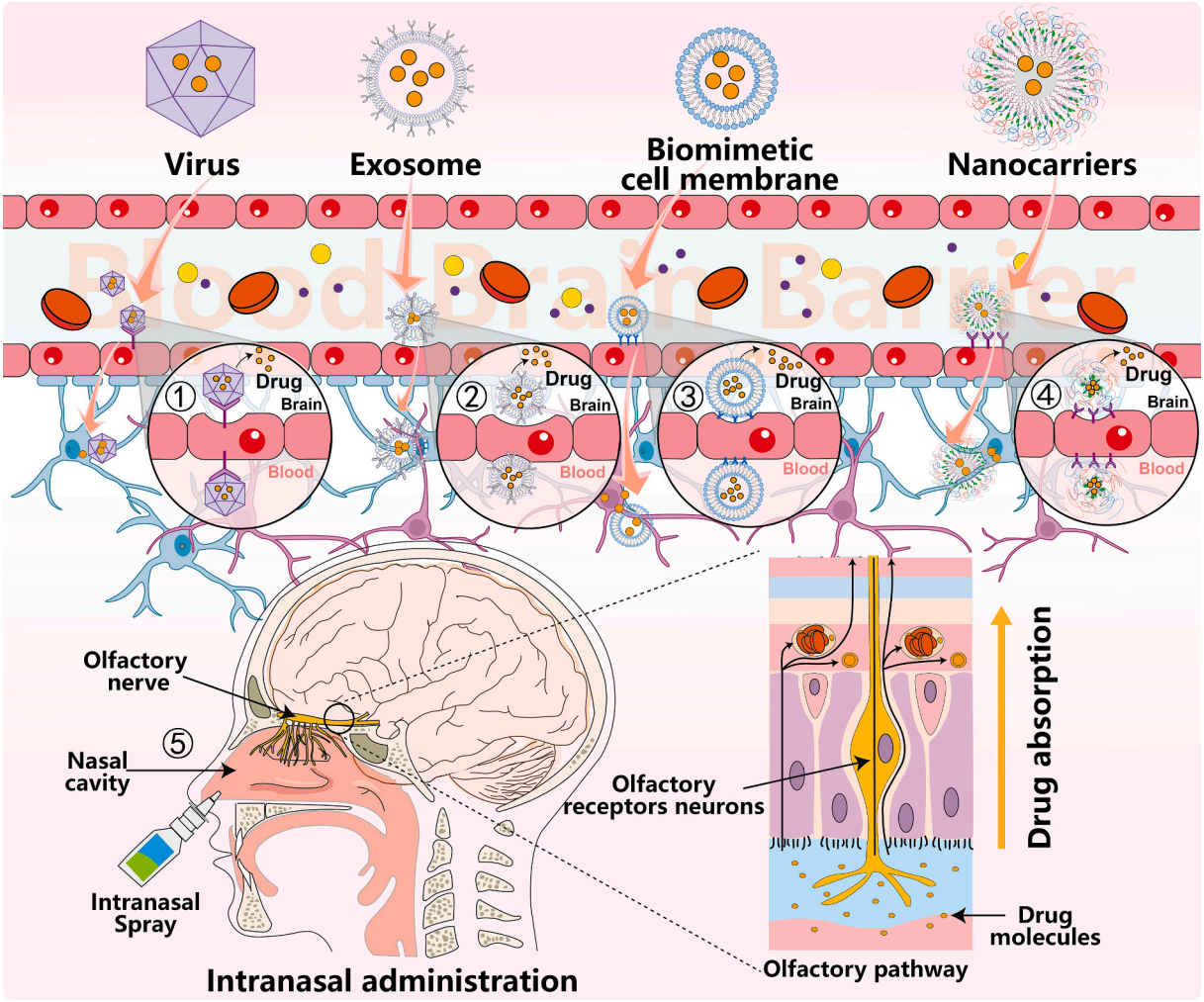


Fig. 4. Effective advanced drug delivery systems to the brain. The non-invasive brain delivery platforms include viral vectors, exosomes, nanocarriers, and cell membrane-based biomimetic systems for CNS-targeted therapy. Intranasal administration provides an additional rapid route for direct drug delivery to the brain.

targeting strategies for CNS-targeted therapy with an extra focus on intranasal administration, aiming to provide potential cutting-edge technologies to deliver PROTACs into the brain (Fig. 4). At the same time, we place particular emphasis on the technical feasibility and potential barriers associated with integrating each platform with PROTACs, thereby laying a foundation for the subsequent discussion of deeper optimization strategies.

3.1. Virus-mediated brain-targeted delivery

The exploitation of viral vectors for CNS delivery builds on more than two decades of translational experience in neurological gene therapy [129]. Viruses possess a natural tropism for nucleic acid transport, providing an evolutionarily optimized platform for cellular entry and gene transduction. Leveraging these intrinsic mechanisms, viral vectors enable efficient, region-specific delivery of genetic payloads across otherwise restrictive neural interfaces. Among available systems, lentivirus, herpes simplex virus (HSV), adenovirus, and adeno-associated virus (AAV) have been most widely investigated, with AAVs emerging as the dominant platform in clinical-stage CNS applications due to their favorable safety profile, long-term expression capability, and relatively low immunogenicity [130,131].

Foust et al. demonstrated the first evidence of systemic rAAV9 delivery achieves trans-BBB targeting with CNS transduction, while Zhang et al. revealed rAAVrh.10 exhibits comparable performance of rAAV9, collectively establishing intravenous AAVs as potent neurotropic vectors [132,133]. Chan et al. developed engineered AAV-PHP.eB and AAV-PHP·S vectors that achieve 40-fold enhanced CNS delivery efficiency with uniform brain distribution via systemic administration in mice, offering a non-invasive strategy for CNS-targeted gene therapy [134]. Huang et al. engineered BI-hTFR1, an AAV capsid targeting human transferrin receptor (TfR1) on the blood-brain barrier. In human TFRC-knockin mice, BI-hTFR1 was actively transported across brain endothelial cells and achieved 40–50-fold higher CNS reporter expression compared to AAV9 [135].

For PROTAC-based strategies, viral vectors are better suited for delivering genetically encoded degraders, such as bioPROTACs, because sustained intracellular production of the degradation machinery can circumvent the physicochemical liabilities associated with small-molecule PROTACs, including high molecular weight and polarity [136,137]. In addition, capsid engineering and the choice of administration route can be leveraged to enhance tropism toward specific CNS cell types and brain regions, thereby aligning with goals of cell-type-selective degradation and, to some extent, improving the therapeutic efficacy and safety window [138]. Despite these innovations, there remain clear limitations to translating viral vectors into PROTAC-related degradation strategies. The immunogenicity of viral capsids and their payloads can elicit dose-dependent toxicity, neuroinflammation, or systemic immune responses that constrain therapeutic windows. In addition, the scalability and cost of manufacturing high-quality, clinical-grade viral vectors pose nontrivial challenges, while species-specific tropism limits the direct translation of optimized serotypes from rodent models to humans [139–141]. Furthermore, achieving precise control over transgene expression levels and regional specificity remains a major bottleneck, as vector biodistribution within the brain can be heterogeneous and influenced by vascular and cellular architecture.

Collectively, viral vector-mediated delivery represents one of the most validated yet imperfect routes for CNS-targeted therapeutics. Continued progress will depend on rational capsid engineering guided by structural virology and receptor mapping, the development of synthetic or hybrid viral-nonviral systems to mitigate immunogenicity, and the implementation of scalable production pipelines. By integrating these strategies, future virus-based platforms may evolve from empirically optimized tools into precision-engineered vehicles for delivering PROTACs and other macromolecular therapeutics to the brain.

3.2. Exosome-mediated brain-targeted delivery

Exosomes are nanoscale extracellular vesicles (30–150 nm) generated through endocytic maturation in multivesicular bodies and released by diverse cellular sources, including neurons, glial cells, endothelial cells, and tumor cells [142]. And they have been engineered as scalable delivery vectors for exogenous genetic cargo and therapeutic agents [143,144]. Brain endothelial cell (EC)-derived exosomes exhibit BBB penetrating capability while preserving cell-cell crosstalk in the brain, amenable to surface engineering for enhanced cellular uptake, positioning them as promising CNS-targeted delivery vectors [145]. Alvarez-Erviti et al. demonstrated systemic delivery of RVG-targeted exosome loaded siRNA achieved 60% mRNA and 62% protein knockdown of BACE1, an AD therapeutic target, in the mouse brain [146]. Similarly, Cooper et al. achieved significant pan-brain reduction of α-synuclein mRNA and protein throughout the brain, the characteristic pathological hallmark of PD, using RVG-exosomes delivering α-synuclein-targeting siRNA [147].

In addition to siRNA, exosomes can also be used to deliver other small molecule drugs to the brain [148]. Yang et al. established brain EC-derived exosomes as carriers for brain-targeted delivery of anticancer drugs doxorubicin and paclitaxel in brain cancer therapy. Tissue plasminogen activator (tPA), a first-line thrombolytic for ischemic stroke, is limited clinically by intracerebral hemorrhage risks upon BBB penetration into brain parenchyma [149]. Khalil et al. engineered Exo-tPA, an exosome-coated tPA/catalase nanoformulation, demonstrating enhanced thrombolytic efficacy, improved tPA stability, and hemorrhage risk reduction compared to free tPA, while maintaining fibrinolytic activity and negligible cytotoxicity [150]. Edaravone (Edv), a neuroprotective agent used in tPA-ineligible stroke patients, is clinically constrained by short half-life, poor BBB permeability, and limited bioavailability [151]. Li et al. developed macrophage-derived exosomes encapsulating Edv to enhance its bioavailability and prolong plasma half-life, with improved brain targeting and reduced neuronal death [152]. Additionally, Guo et al. leveraged plasma-derived Edv-exosomes to enhance its short-term functional and histological outcomes via transferrin receptor-mediated brain targeting [153].

Collectively, these studies underscore the potential of exosomes as next-generation CNS delivery platforms. The advantage of exosomes as carriers for PROTAC delivery lies in their membrane-enclosed architecture, which can protect the payload to a certain extent, improve in vivo stability and biodistribution, and through surface engineering, enhance brain targeting and cellular uptake within the CNS [154,155]. Nonetheless, critical challenges remain before clinical translation can be realized. The large-scale production of exosomes with consistent purity, integrity, and bioactivity remains technically demanding [148]. Heterogeneity in exosome composition, arising from differences in source cells, isolation methods, and purification standards, complicates reproducibility and regulatory evaluation. Moreover, potential immunogenicity, particularly in immunocompromised or repeatedly dosed patients, requires careful assessment.

Therefore, in CNS-PROTAC applications, exosomes are better positioned as strategically engineered biomimetic carriers: on one hand, their ability to traverse the BBB and interact efficiently with cells can increase the likelihood of effective brain delivery. On the other hand, successful translation will require reproducible manufacturing and rigorous quality control, and their true benefit should be evaluated by intracellular degradation endpoints rather than brain concentration alone [155]. Through these coordinated advances, exosomes could mature from experimental nanocarriers into clinically viable, precision-engineered vehicles for targeted PROTAC and macromolecular delivery to the brain.

3.3. Nanocarriers-mediated brain-targeted delivery

Nanocarriers, typically ranging from 1 to 300 nm, are colloidal

systems capable of encapsulating and protecting therapeutic agents from degradation while modulating their pharmacokinetic profiles. With the rapid evolution of nanotechnology, these nanoscale platforms have emerged as versatile vehicles for crossing the BBB, owing to their tunable physicochemical properties, surface functionalization potential, and ability to exploit endogenous transport pathways [156,157]. Collectively, nanocarrier-mediated delivery systems markedly enhance the brain penetration, stability, and bioavailability of diverse therapeutic modalities, encompassing polymeric, inorganic, and lipid-based nanoparticles [158–161].

Importantly, for CNS-directed PROTAC development, BBB transport represents only the first bottleneck. Nanocarriers can be engineered not only to improve cellular uptake into relevant neural cell types but also to promote endosomal escape to enable cytosolic availability, both of which are essential for productive ternary complex formation and ubiquitin-proteasome-mediated degradation. In this context, delivery platforms should be evaluated not only by brain exposure but also by their ability to enhance intracellular free concentration and overcome endosomal sequestration, thereby strengthening the causal chain from delivery to degradation and efficacy.

3.3.1. Polymeric nanoparticles

Polymeric nanoparticles (PNPs) are nanosized, homogeneous spheres *co*mposed of biocompatible and biodegradable polymers, including polysaccharides, proteins, poly(butylcyanoacrylate) (PBCA), poly(lactic-co-glycolic acid), poly(lactic acid), and poly(caprolactone) (PCL), that encapsulate or surface-conjugate therapeutic agents [162–172]. The prominent advantages of PNPs are enhanced mechanical stability contributing to prolonging circulation and the flexible outer layer that offers multiple conjugating sites for an efficient targeting. For instance, polysorbate 80-coated PBCA nanoparticles exhibit enhanced CNS penetration [164,173,174]. Xin et al. engineered ANG-NP (PEG-PCL nanoparticles conjugated with Angiopep), a dual-targeting nanoparticle system engaging LRP receptors on the BBB and glioma cells, to enhance chemotherapeutic transport across the BBB and tumor tissue penetration [171]. Advances in polymer and surface engineering enable polymeric nanoparticles to deliver diverse cargoes, from small molecule drugs to nucleic acids, proteins, and diagnostics [175–177]. Chitosan, a natural biodegradable and biocompatible polysaccharide capable of forming nanoparticles, enables systemic CNS delivery of peptides (amyloid-beta subfragments), dopamine, and caspase inhibitors [178–181]. The major challenges to clinical translation of PNPs system is the ability to scale-up this system in a cost-effective manner.

3.3.2. Inorganic nanoparticles

Inorganic nanoparticles (INPs) exhibit tunable size, shape, surface charge, and functionalization, enabling BBB penetration and enhanced drug delivery [182]. Metal-based NPs, derived from noble metals like gold, silver, and platinum leverage unique size, surface reactivity, magnetic and thermal properties, contributing to their potential for crossing the BBB, enabling targeted drug delivery, diagnostic and therapeutic applications in neurological disorders. Gold nanoparticles (AuNPs) have emerged as promising biomedical platforms due to the unique optical and thermal properties, enabling targeted delivery of biomolecules (genes/proteins/drugs). Their optical signatures arise from localized surface plasmon resonance (LSPR), exhibiting size and shape-dependent absorption and scattering modulated by local refractive index and aggregation states [183,184]. AuNPs' size, morphology, and surface functionalization dictate BBB penetration and brain delivery [185]. Betzer et al. demonstrated 20 nm insulin-coated gold nanoparticles (INS@AuNPs) exhibited systemic-wide dispersion with maximal brain accumulation [186]. Similarly, Kang et al. reported deeper brain penetration of 10 nm Alexa Fluor 633-labeled AuNPs compared to 50 or 100 nm counterparts. Recent study reported that PEGylated AuNPs reduce immune response while enhancing cellular uptake, serving as promising candidates for BBB-penetrant drug delivery [187]. Carbon-based nanoparticles (CNPs), introduced into drug delivery systems recently, combine functionalizable surfaces, high surface area, low toxicity, and ultrasmall size to enable BBB-penetrant drug delivery [188]. CNPs, including graphene, carbon nanotubes (CNTs), Carbon dots (CDs), serve as versatile brain-targeted drug carriers. Their unique architectures enable applications in drug and gene delivery, tissue engineering, cellular imaging, and biosensing [189]. Overall, INPs are transforming neurological medicine by enabling targeted drug delivery via distinct physicochemical properties, size, shape, surface modifications, to enhance BBB penetration and therapeutic efficacy [190]. Clinical translation requires addressing safety risks, including cytotoxicity, oxidative stress, systemic accumulation, through rigorous nanoparticle optimization, size, charge, surface properties, to mitigate hazards [191,192].

3.3.3. Lipid-based nanoparticles

Lipid-based nanoparticles (LBNs), including liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and nanoemulsion have been developed to CNS disease [193,194]. These systems demonstrate high physical stability, substantial versatility in encapsulating hydrophilic and lipophilic therapeutics, and enhanced BBB penetration for CNS disease treatment [195,196]. Liposomes feature a hydrophilic core enclosed by hydrophobic lipid bilayers, enabling dual encapsulation of hydrophilic therapeutics (e.g., drugs, DNA) and hydrophobic compounds through their amphiphilic structure [197,198]. Surface-engineered liposomes, functionalized with polymers, polysaccharides, or targeting ligands, enhance systemic blood circulation and targeting precision [198–200]. Xiang et al. engineered Chlorotoxin (ClTx)-modified stealth liposomes (ClTx-LS) loaded with levodopa (LD) for PD targeting. ClTx functionalization enhanced brain endothelial cell uptake in vitro and elevated dopamine levels in the substantia nigra and striata in vivo [201]. Yang et al. developed transferrin-Pep63-liposomes (Tf-Pep63-Lip), Tf-modified liposomes encapsulating Pep63, a neuroprotective peptide preserving synaptic plasticity and memory, to reduce hippocampal Aβ burden and ameliorate cognitive deficits in AD [202]. Gu et al. reported that liposomes coupled with PEG (PEG-ATX@NPs) enhance astaxanthin's water-solubility bioavailability, and therapeutic efficacy while enabling brain-targeted drug delivery [203]. SLNs, with a phospholipid-coated hydrophobic core, encapsulate both hydrophilic and hydrophobic drugs like liposomes, enabling precise, targeted delivery to specific tissues [204,205]. SLNs have been successfully utilized to deliver quercetin and sesamol to improve cognitive impairment [206–208]. The crystalline structure of SLNs limits drug loading and triggers crystallization-driven drug expulsion during storage [209,210]. NLCs were developed to overcome the limitations associated with SLNs. NLCs and SLNs share morphology, but NLCs enable superior drug release through higher encapsulation efficiency and storage stability, along with enhanced biocompatibility and manufacturability over SLNs [209]. Raju et al. developed berberine-loaded NLCs (Berb-NLCs) targeting $AlCl_3$-induced AD rats, demonstrating acetylcholinesterase inhibition, Aβ reduction, antioxidant effects, and cholesterol modulation [211]. Nanoemulsions offer a simpler alternative to SLNs and are easier to manufacture. Silva et al. engineered a Cannabidiol (CBD) nanoemulsion to mitigate its high lipophilicity and low oral bioavailability, enhancing therapeutic efficacy in autism spectrum disorder (ASD). Advanced lipid-polymer hybrid nanoparticles synergistically combine lipid and polymeric systems to enhance functional performance [212]. Darwish et al. engineered piperine-loaded chitosan-lipid nanoparticles (PP-CLNPs) to optimize piperine delivery for cognitive enhancement applications [213]. Collectively, biocompatible nanocarriers endowed with tunable physicochemical and surface properties represent an integrated strategy to overcome the neurovascular barrier, enabling precise, sustained, and cell-specific delivery within the brain. By uniting molecular encapsulation, surface engineering, and biological mimicry, these systems not only advance CNS pharmacology but also establish a translational foundation for the next generation of brain-penetrant PROTAC

therapeutics.

3.3.4. Advancing brain-targeted nanocarriers from BBB transport to intracellular delivery

Mechanistically, nanocarriers enhance cellular uptake through leveraging multiple design variables that often operate synergistically [214]. Surface charge can modulate electrostatic interactions with cellular membranes, while membrane-interactive components (such as fusogenic lipids) and cell-penetrating peptides (CPPs) can promote uptake and intracellular trafficking [215,216]. Moreover, ligand functionalization enables receptor-mediated transcytosis across the BBB and subsequent cellular internalization within the brain, including targeting pathways such as transferrin receptor (TfR), LDL receptor family members (LRP1/LDLR), and insulin receptor [217–219]. However, even after successful internalization, PROTACs still face the fate of degradation within endosomes, making endosomal escape a second rate-limiting step. To address this, platforms may incorporate pH-responsive materials (acid-triggered destabilization), proton-sponge polymers (osmotic swelling and membrane disruption), or fusogenic lipids/peptides (membrane fusion/perturbation) to increase cytosolic release [220–222]. Furthermore, cell-type selectivity is particularly critical in the CNS, as neurons, astrocytes, microglia, and oligodendrocytes differ in receptor expression and uptake propensity, which can strongly influence both efficacy and safety [214]. Gao et al. highlighted that a cascade targeting strategy can further enhance specificity, where angiopep-2 peptide is first used to mediate blood-brain barrier penetration, followed by EGFP-EGF1 protein to target glial cells, thereby achieving precise delivery to specific cell types within the brain [223]. These benefits must be balanced against translational considerations such as immunogenicity, long-term brain accumulation, and carrier-associated toxicity, as well as the requirement that released PROTACs remain chemically stable and pharmacologically competent after unloading [224,225].

In summary, the development of multifunctional nanoplatforms is advancing the intracerebral delivery of PROTACs from a singular across-barrier perspective to a systematic solution that simultaneously addresses cellular uptake, endosomal escape, and cell-type targeting. This holds promise for overcoming the delivery bottlenecks of PROTACs in the treatment of central nervous system disorders, thereby unlocking their full potential as a protein degradation therapy.

3.4. Cell membrane based biomimetic vehicles-mediated brain-targeted delivery

Cell membranes have emerged as natural multifunctional biomaterials with intrinsic potential for surface engineering and targeted delivery design. Nanoparticles cloaked with cellular membranes, collectively referred to as cell membrane-based biomimetic vehicles, recapitulate host-derived surface architectures that provide superior biocompatibility, immune evasion, and extended systemic circulation [226–228]. By presenting native proteins, lipids, and glycans, these biomimetic carriers minimize immunogenicity and toxicity while maintaining the biological stealth of their cellular counterparts, making them a central focus in next-generation drug delivery research [229,230].

In addition, the conjugation of specific targeting ligands or receptors to the membrane surface can further enhance tissue and cell-type specificity. However, this functionalization must be carefully controlled to preserve the membrane's native structural and compositional integrity, since disruption of its architecture can compromise both stability and biomimetic fidelity. The fabrication of cell membrane-coated nanoparticles generally involve three sequential processes, including membrane isolation, nanoparticle preparation, and subsequent fusion of the two components. Membranes from enucleated cells such as erythrocytes and platelets are usually obtained through repeated freeze-thaw cycles followed by differential centrifugation [231]. In contrast, isolating membranes from nucleated cells such as tumor cells, macrophages, natural killer cells, and neutrophils requires cell lysis, homogenization, and gradient centrifugation to preserve functional proteins. The purified membrane vesicles are then fused with preformed nanoparticle cores through physical extrusion, ultrasonication, or microfluidic mixing to yield hybrid nanostructures that combine the functional complexity of biological membranes with the versatility of synthetic nanomaterials [232]. These biomimetic platforms bridge the gap between natural and engineered delivery systems. Their capacity to integrate biological specificity with nanoscale precision offers a transformative path toward the development of next-generation therapeutics for brain-targeted applications.

Building upon the principles of biomimetic design, the interaction between cell membrane-coated nanoparticles and the brain microvascular endothelium represent a pivotal determinant of BBB penetration efficiency. The inner surface of cerebral blood vessels is primarily composed of brain microvascular endothelial cells (BMECs), and recognition of these cells is a crucial prerequisite for trans-BBB transport following systemic administration. The inherent lipophilicity and biological compatibility of cellular membranes facilitate the uptake of biomimetic vehicles by BMECs through membrane fusion and endocytosis, thereby promoting efficient drug translocation into the brain parenchyma.

To further enhance the BBB-penetrating ability of membrane-based biomimetic carriers, two major design principles have emerged: the strategic selection of membrane sources and the functional modification of their surfaces. Conventional membrane sources include erythrocytes, platelets, neutrophils, macrophages, mesenchymal stem cells, and tumor cells, each contributing distinct biological functions such as immune evasion, prolonged circulation, or inflammation targeting [233]. In parallel, increasing attention has been directed toward membranes derived from CNS-related cells, including astrocytes, microglia, oligodendrocytes, cortical neurons, and brain endothelial cells [234,235]. These CNS-origin membranes exhibit superior homotypic targeting and tissue compatibility, markedly improving BBB crossing efficiency and intracerebral accumulation. For instance, Wang et al. engineered a BMEC-targeted biomimetic vehicle using membranes derived from bEnd.3 cells. Upon intravenous administration in mice, this carrier demonstrated substantially greater BBB permeability and glioblastoma localization compared with traditional tumor membrane-coated systems [235]. Collectively, these advances underscore the critical importance of membrane source selection and functional adaptation in dictating the translocation behavior of biomimetic nanocarriers. Expanding the repertoire of CNS-derived membrane materials, coupled with precision surface engineering, is poised to redefine the design framework for next-generation BBB-penetrant delivery systems.

Although membranes derived from brain tissue or CNS-resident cells offer superior biological homology, their acquisition remains technically challenging and raises practical and ethical concerns for clinical application [236]. Consequently, functional modification of conventionally sourced membranes has emerged as a more feasible and controllable strategy to enhance the BBB-penetrating ability of biomimetic vehicles. Among the most effective ligands, the rabies virus glycoprotein-derived peptide RVG facilitates transcytosis by binding to nicotinic acetylcholine and GABA(B) receptors expressed on brain endothelial cells, thereby promoting receptor-mediated BBB transport [237,238]. Another representative ligand, triphenylphosphine (TPP), serves as a mitochondria-targeting moiety that exploits the organelle's negative membrane potential to achieve subcellular specificity [239]. Han et al. demonstrated the potential of integrating these targeting elements by coating resveratrol-loaded nanoparticles with red blood cell membranes and subsequently inserting DSPE-PEG2000-conjugated RVG and TAT peptides into the outer membrane layer [240]. The resulting biomimetic construct efficiently traversed the BBB, accumulated in brain mitochondria, attenuated mitochondrial reactive oxygen species, and conferred marked neuroprotective effects.

For CNS delivery of PROTACs, the central advantage of biomimetic systems lies in their homologous targeting capability. This biomimetic strategy can reduce immune clearance and prolong circulation time, while the compositional complexity of membrane proteins helps mimic endogenous transport pathways. Moreover, the choice of membrane source can confer features such as cell type-specific targeting and inflammation tropism, allowing the biomimetic membrane to function as an upstream "navigation layer" for PROTACs that synergizes with the drug-loading and controlled-release functions of the nanoparticle core [241]. Despite these advances, the therapeutic translation of cell membrane-based biomimetic vehicles for CNS disorders remains in its infancy and faces several critical challenges. The limited availability of primary human cell membranes continues to restrict large-scale and standardized manufacturing. Maintaining the structural integrity of isolated membranes and the functional activity of embedded proteins over extended storage periods also poses substantial technical barriers. Looking forward, the integration of precision membrane engineering, synthetic biology, and scalable biomanufacturing may overcome these limitations and transform biomimetic nanocarriers from experimental constructs into clinically viable platforms. Such convergence would not only accelerate their translation into CNS therapeutics but also establish a conceptual foundation for next-generation brain-targeted delivery systems that harmonize biological authenticity with engineering precision.

3.5. Intranasal delivery as a noninvasive route for brain-targeted PROTAC therapeutics

Intranasal administration provides a noninvasive and rapid route for direct drug delivery to the brain by utilizing the olfactory and trigeminal neural pathways. This approach bypasses the BBB and avoids hepatic first-pass metabolism, thereby reducing systemic toxicity while achieving rapid therapeutic access to the CNS [242–244]. Drugs delivered intranasally can reach the olfactory bulb through extracellular diffusion or axonal transport and subsequently distribute to higher brain regions [16,245]. The efficiency of nose-to-brain delivery depends on the physicochemical characteristics of the drug, formulation design, and the optimization of delivery devices. Small molecules and lipophilic agents readily permeate the nasal mucosa, whereas macromolecules such as peptides, proteins, and genes show limited permeability, which necessitates formulation strategies to improve mucosal adhesion and penetration.

Conventional nasal formulations are constrained by low permeability and rapid mucociliary clearance. In contrast, nanotechnology-enabled intranasal systems including nanoemulsions, polymeric nanoparticles, liposomes, and exosomes have transformed the paradigm of nose-to-brain delivery by improving drug stability, residence time, and cerebral accumulation. These nanosystems enhance epithelial transport through mucoadhesive polymers and ligand-mediated transcytosis while protecting therapeutics from enzymatic degradation [246–248]. Several studies have illustrated these advances. Huang et al. developed a thermoresponsive hydrogel for the controlled release of mesenchymal stem cell-derived extracellular vesicles, achieving prolonged nasal retention and improved efficacy in AD [249]. Liu et al. designed a black phosphorus nanocarrier encapsulating methylene blue within a thermoresponsive gel, which exhibited efficient brain delivery and cognitive restoration in tauopathy models [250]. García-Pardo et al. reported dopamine-loaded nanoscale coordination polymers that achieved targeted nigrostriatal delivery and improved outcomes in PD [251]. Collectively, these innovations demonstrate the translational potential of intranasal nanoplatforms for central nervous system disorders.

The physicochemical and pharmacokinetic properties that limit the systemic delivery of PROTACs, including their high molecular weight, polarity, and susceptibility to hepatic metabolism, also make them promising candidates for intranasal administration. The direct neural transport enabled by this route can bypass systemic clearance and the blood-brain barrier, allowing PROTACs to reach intracerebral targets without extensive structural modification. Incorporating PROTACs into nanostructured intranasal carriers such as lipid-polymer hybrids or thermoresponsive gels can further enhance solubility, stability, and local retention, promoting sustained diffusion along the olfactory and trigeminal pathways. This strategy provides an opportunity to integrate the catalytic protein degradation mechanism of PROTACs with localized and noninvasive delivery to the brain, thereby minimizing systemic exposure and potential off-target toxicity.

Intranasal administration provides a unique BBB-bypassing route for PROTACs, with the potential to reduce reliance on conventional BBB permeability and to mitigate the insufficient brain exposure often observed after systemic dosing due to the high molecular weight and polarity of PROTACs. Its advantages include rapid onset, improved patient compliance, and the possibility of reducing systemic adverse effects. Although challenges remain, including dosing limitations, formulation reproducibility, and interspecies anatomical variability, the convergence of intranasal nanotechnology with targeted protein degradation represents a promising frontier for neurotherapeutic development. Future efforts in formulation engineering, ligand-guided nose-to-brain targeting, and pharmacokinetic modeling will be essential to translate intranasal PROTAC delivery from conceptual promise to clinical reality.

3.6. Subcellular targeting and compartmentalized delivery

For certain CNS-directed PROTACs, effective target degradation is not restricted to the cytosol but may require access to specific organelles or membrane-associated compartments. Accordingly, beyond facilitating BBB transport, subcellular targeting , including delivery to the nucleus as well as mitochondria, endoplasmic reticulum, and lysosomes, is increasingly viewed as a frontier strategy to expand the degradable target space and to enhance pharmacological selectivity. Common approaches to nuclear delivery include introducing or exposing nuclear localization signals (NLSs) on the carrier surface or on releasable components, together with optimization of particle size, morphology, and surface chemistry to better accommodate nuclear pore transport and nuclear import mechanisms, thereby increasing nuclear accumulation [252]. When disease-relevant pathways involve mitochondrial dysfunction, a mitochondrial-targeting design can be further incorporated, for example by using membrane potential-driven cationic ligands (such as TPP) or other mitochondria-targeting motifs to enrich payloads within this organelle [253]. However, mitochondrial targeting requires a careful balance between enrichment efficiency and potential liabilities such as membrane perturbation and oxidative stress, and these concerns are particularly salient in neurodegenerative indications where chronic dosing may be required and long-term safety is paramount [254]. For targets that are difficult to address with conventional PROTACs, such as membrane proteins or extracellular proteins, recent strategies that leverage the lysosomal degradation pathway (e.g., LYTACs) have emerged. Conceptually, these modalities hijack receptor-mediated endocytosis to traffic the target protein to lysosomes for degradation, providing a route that is complementary to proteasome-driven degradation in terms of compartmental choice [255]. Collectively, the lysosome-targeting paradigm also underscores a broader principle for CNS delivery-platform design: subcellular targeting is not limited to delivering drugs into the cytosol/nucleus, but may also entail selectively engaging organelle-specific degradation axes to broaden the degradable target spectrum and the actionable subcellular space.

In conclusion, current non-invasive delivery platforms constitute a rapidly expanding toolbox for advancing CNS therapeutics. However, they also highlight a central translational reality: no single delivery vehicle is universally optimal. Successful development of CNS-directed PROTACs will likely require a personalized, mechanism-guided strategy that aligns the degrader's physicochemical properties with target biology and the disease context. Given the challenges imposed by the

distinctive physicochemical profiles and mode of action of PROTACs, mere physical crossing is no longer sufficient to meet therapeutic demands. Instead, a key priority for the field is to build the most appropriate delivery system on the basis of the platforms described above, and to rationally co-optimize brain-targeting efficiency, intracellular fate, and safety through integrated design. Accordingly, the next section focuses on recent progress in solution development and overall developability, summarizing current approaches to improve PROTAC brain bioavailability through rational structural optimization and strategic selection of innovative delivery platforms, with the goal of providing both conceptual guidance and practical pathways to overcome translational bottlenecks in CNS disorders.

4. Effective strategies for PROTACs delivery to the brain

PROTACs offer potent targeting of non-therapeutic brain proteins, yet targeted brain delivery remains a key barrier to their therapeutic application in CNS disorders. The previous section systematically summarized recent advances in brain delivery systems and provided an initial assessment of the technical feasibility and inherent limitations of integrating each platform with PROTACs, thereby catalyzing the development of new brain-targeting strategies. However, platform availability does not necessarily equate to optimality. To truly overcome the translational bottlenecks facing PROTACs in CNS disorders, platform selection must be coupled with rational design and systematic optimization to improve delivery efficiency, precision, and safety. Accordingly, this section focuses on these considerations and provides an in-depth discussion of current approaches to enhance PROTAC brain bioavailability through rational structural optimization and innovative delivery platforms. Building on the toolbox outlined in the previous section, we emphasize recent progress on how these platforms can be strategically leveraged to maximize the therapeutic potential of PROTACs.

4.1. Chemical structure optimization for PROTACs brain-targeted delivery

Canonical PROTACs are heterobifunctional molecules composed of a protein of interest (POI) ligand and an E3 ligase ligand via a suitable linker, resulting in high molecular weight. Rational chemically design could enhance the BBB permeation efficiently. Key strategies to enhance BBB permeability and minimize efflux include enhancing lipophilicity, reducing hydrogen bond donors (HBD), lowering polar surface area (tPSA) via charge modification, decreasing pKa by removing basic groups, and introducing conformational constraints to boost molecular rigidity [256]. CRBN and VHL currently serve as the predominant E3 ligases in PROTACs design. Generally, CRBN-based PROTACs are prioritized due to their lower molecular weight (MW) and reduced rotatable bond (RB) counts compared to VHL-based counterparts, thereby optimizing PK profiles and enhancing BBB penetration efficiency [257,258].

Ren et al. developed novel benzisoxazole-derived CRBN ligands, C-1 and C-2, exhibiting enhanced CRBN binding affinity and reduced immunomodulatory effects versus thalidomide analogues. And their reduced molecular weight and tPSA result in improved solubility and metabolic stability [259]. When designing POI ligands, it is possible to preserve high-affinity target binding while enhancing BBB penetration via rational structural modifications. Chemically modify small molecules into a more lipophilic analog can enhance the BBB permeation, as exemplified by the addition of a methyl group to morphine to produce codeine, achieving 10-fold higher BBB permeability [260]. Radaram et al. demonstrated that a fluoroethyl moiety addition of crizotinib (an anaplastic lymphoma kinase inhibitor with negligible BBB penetration) enhances lipophilicity and brain permeability [261]. However, given PROTACs' inherently high log*P* and the ideal range for BBB permeability has been found to be 1.5–4, lipophilic group addition remains selectively applicable [256,262]. Lipinski's rule of five specifies hydrogen bond donors (HBDs) <5 for drug candidates, while CNS drugs typically require <3. Emerging evidence highlights HBD reduction as a key strategy to enhance BBB penetration in drug design. Dighe et al. reported that intramolecular hydrogen bonds concealed the polar hydroxy and tertiary amine groups of compounds 11 and 12, which exhibited a permeability higher than that of 13 without intramolecular hydrogen bonding [263]. Beyond E3 ligase and target protein ligands modification, linker design critically determines PROTACs BBB permeability, and optimizing linker type, length, and rigidity represents a key design strategy to enhance brain penetration [65]. PEG-based linker serves as the predominant one in PROTAC development, enhancing aqueous solubility and modulating cellular permeability to impact oral absorption. Monsen et al. substituted the flexible PEG linker with rigid heterocycles in PROTAC design, improving degradation efficiency. Structural rigidity enhances lipophilicity and BBB permeability, exemplified by degrader NU227326 with prolonged brain retention [264]. Arvinas has pioneered ARV-102, the first orally bioavailable leucine-rich repeat kinase 2 (LRRK2)-targeting PROTAC degrader, which utilized cyclohexane-based linker, demonstrating BBB penetration and CSF LRRK2 reduction, now advancing through Phase 1 clinical trials. Liu et al. engineered XL01126, a novel LRRK2-targeting PROTAC, by substituting morpholine with piperazine to optimize linker conjugation, achieving oral bioavailability and BBB penetration via oral or parenteral administration in mice [32]. Overall, optimal linker selection for PROTACs is scaffold-specific, necessitating holistic lipophilicity assessment during design. Recently, Zhang et al. engineered a linker-free PROTAC using single amino acid degradation tags (Pro-BA), achieving enhanced hydrophilicity, reduced molecular weight, and improved pharmacokinetics and oral bioavailability in mice, opening new avenues for brain-targeted PROTAC design [265].

In conclusion, the chemical optimization of PROTAC components, including E3 ligase ligands, linker design, and target protein ligands, plays a pivotal role in enhancing BBB permeability, solubility, and bioavailability. These structural modifications are essential for improving the PK profiles of PROTACs and enabling efficient brain-targeted delivery. However, further studies on the structure-activity relationships (SAR) of PROTACs are required to fully elucidate the mechanisms by which chemical modifications influence CNS delivery. Understanding these relationships will provide critical insights into the development of more effective PROTAC-based therapies.

4.2. PROTAC delivery systems for neurodegenerative diseases

While rational molecular optimization can substantially enhance the degradation efficiency, selectivity, and drug-likeness of PROTACs, such improvements alone remain insufficient to overcome the formidable physiological barriers of the CNS. The intrinsic physicochemical complexity of PROTACs, characterized by high molecular weight, large polar surface area, and limited membrane permeability, inevitably constrains their brain exposure even after extensive structural refinement. Thus, achieving therapeutic efficacy for NDs requires the convergence of chemical innovation with advanced delivery technologies capable of facilitating efficient BBB traversal and sustained target engagement within neural tissues.

Although delivery strategies for CNS therapeutics have been extensively explored, their specific adaptation to PROTACs is still in its nascent phase. Current research primarily centers on two promising modalities: cell-penetrating peptide (CPP)-mediated systems, which leverage peptide motifs to enhance intracellular uptake and BBB penetration, and NPs-based delivery systems, which utilize nanoscale engineering to encapsulate, protect, and transport PROTACs into the brain. These early frameworks represent not only experimental proof-of-concept for brain-targeted PROTAC delivery but also a foundational step toward integrating molecular design with precision pharmacological delivery. As the field advances, such hybrid chemical-biological systems are poised to redefine the boundaries of targeted protein

degradation in the treatment of neurodegenerative diseases.

4.2.1. CPP-mediated delivery systems

CPPs are short peptides characterized by their high efficiency in traversing cell membranes and their ability to transport bioactive molecules larger than themselves into cells [266,267]. Owing to their high transmembrane efficiency and relatively straightforward design, CPP-mediated delivery systems represent a significant strategy for the brain delivery of PROTACs. Based on their origin and properties, CPPs are mainly categorized into two classes: natural sequences derived from viruses or native proteins, such as the transmembrane domain of the TAT protein derived from the HIV-1 and Penetratin derived from the Drosophila Antennapedia homeodomain, and artificial synthetic sequences obtained through rational design or screening, such as polyarginine or polylysine-based CPPs [268–273]. Their precise mechanism of entering the cell is not fully elucidated but is known to primarily involve both energy-dependent endocytosis and energy-independent direct penetration [274,275]. In the design of peptide-based PROTACs, conjugation to CPPs can enhance the ability of PROTACs to cross both the BBB and cell membranes, thereby increasing their bioavailability in the brain.

In AD, neurofibrillary tangles formed by hyperphosphorylated Tau protein are a major driver of disease progression. Under physiological conditions, Tau is a microtubule-associated protein that primarily regulates microtubule stability and intracellular transport in neurons by binding to microtubules and undergoing appropriate post-translational modifications [276]. However, under the pathological conditions of AD, Tau protein undergoes aberrant phosphorylation at multiple sites, leading to its dissociation from microtubules and subsequent intracellular self-assembly into paired helical filaments (PHFs) predominantly composed of β-sheet structures [277]. These highly aggregated Tau pathological filaments severely disrupt intracellular transport, further leading to synaptic dysfunction and neuronal toxicity, ultimately resulting in cognitive decline. To target this pathogenic protein, Chu et al. designed a CPP-based PROTAC molecule, TH006 [20]. This molecule consists of a Tau-recognizing fragment (YQQYQDATADEQG), a GSGS linker, a fragment (ALAPYIP) that binds the E3 ligase (VHL), and a C-terminal fused CPP, Poly-D-arginine (R8). The results demonstrated that TH006 could effectively penetrate the BBB, significantly reduce Tau levels in an AD mouse model, and mitigate Aβ-induced cytotoxicity. This study represents the first report of peptide-directed ubiquitin-proteasome degradation of endogenous Tau protein, opening a novel therapeutic avenue for AD. These data underscore the considerable potential of CPP-mediated PROTAC delivery systems for treating NDs. Such systems can efficiently promote cellular internalization, effectively overcome biological barriers, and achieve specific degradation of target proteins in the brain. However, challenges remain for the large-scale clinical application of this strategy, including the lack of tissue specificity of CPPs potentially leading to off-target effects in peripheral tissues, and the susceptibility of CPPs to proteolytic degradation in vivo, necessitating optimization of their pharmacokinetic properties [275,278,279]. Future research could focus on further optimizing CPP sequences, fusing membrane-penetrating peptides with targeting peptides to develop brain-targeted delivery systems, or combining them with other delivery strategies to create synergistic combination approaches.

4.2.2. NPs-based delivery systems

As previously mentioned, NPs-based delivery systems offer a highly promising avenue for addressing the challenge of brain delivery, and studies have begun applying them to PROTACs for NDs. Gong et al. reported the first study utilizing NPs to deliver PROTACs across the BBB for AD therapy [280]. The team developed a Tau-targeting Neurotransmitter-Derived Lipidoids (NT-lipidoids)-PROTACs-DNA Nanocomplex, constructed via electrostatically guided self-assembly and DNA intercalation. The core strategy involves using negatively charged calf thymus DNA as a bridging molecule to neutralize the partial positive charge of the PROTAC, enabling its effective encapsulation by similarly positively charged NT-lipidoids, ultimately leading to the self-assembly of a stable nanocomplex approximately 100 nm in size. Experimental results indicated that following tail vein injection, this nanocomplex exhibited superior BBB penetration capability, efficiently degraded Tau protein, and improved cognitive function in AD mice. Compared to unformulated PROTAC, the NPs-encapsulated PROTAC demonstrated prolonged retention in the brain, enhanced degradation efficiency, and a reduced required dose, highlighting the advantages of this nano-delivery system in enhancing the brain delivery of PROTACs and laying a solid foundation for its further clinical translation.

Furthermore, Ge et al. innovatively developed a novel brain-targeted delivery system-a TfR-based DNA nanoflower [281]. DNA nanoflowers are flower-like DNA nanomaterials prepared by rolling circle amplification, whose excellent biocompatibility and biodegradability make them ideal drug delivery carriers [282,283]. In this study, the team designed a specific RNA Oligo-PROTAC (dFUS-E9C) targeting the FUS protein and loaded it into brain-penetrating DNA nanoflowers carrying hundreds to thousands of copies of TfR-engaging aptamers, forming an integrated delivery system termed FRONTAC^{FUS}. The FUS protein is an RNA-binding protein, whose mutation leads to abnormal cytoplasmic aggregation, causing amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) [284,285]. The FRONTAC system demonstrated remarkable BBB traversal capability. In vivo imaging showed that FRONTACFUS reached the brain parenchyma within 2 h of tail vein injection, whereas the control dFUS-E9C lacking TfR targeting failed to cross the BBB. This result indicates that TfR-mediated transcytosis is the key mechanism for the brain delivery of the FRONTAC system. Moreover, FRONTAC^{FUS} significantly reduced FUS protein levels by 50%–70% in mouse brains within 24 h, with the degradation effect lasting over two weeks, and did not induce significant neurotoxicity or peripheral organ toxicity. Using FUS protein degradation as a proof-of-concept, this study validates the potential of DNA Nanoflower-based PROTAC delivery systems for treating NDs, thereby providing a versatile paradigm for the broader application of this technology.

In summary, although current delivery strategies for PROTACs targeting NDs are limited, the existing approaches based on CPP and NPs each demonstrate distinct advantages and considerable promise. CPP systems are simple and efficient, lipidoid-based nanocarriers offer good biocompatibility and functional flexibility, and TfR-based DNA nanoflowers provide precise targeting and high loading capacity. Future research should focus on enhancing brain-targeting efficiency and specificity, optimizing safety and pharmacokinetic profiles, addressing scale-up manufacturing challenges, and exploring the application of other delivery systems. As these technologies mature and advance through clinical translation, PROTAC technology holds the potential to deliver substantive therapeutic breakthroughs for patients with NDs such as AD, PD, and ALS, which currently lack effective treatments.

4.3. PROTAC delivery systems for other brain disorders

While delivery strategies based on CPP and NPs offer promising solutions for delivering PROTACs to treat NDs like AD, their applicability extends far beyond. In recent years, PROTACs have been extensively explored for other brain diseases, particularly within the realm of brain tumors, with a significant focus on malignant gliomas such as glioblastoma (GBM). Compared to NDs, brain tumor therapy similarly faces severe and concurrent challenges, including BBB penetration, tumor heterogeneity, an immunosuppressive microenvironment, and chemoresistance [111,286–288]. Traditional monotherapies often fall short, whereas PROTAC technology can precisely degrade key oncoproteins, theoretically enabling fundamental intervention of core tumorigenic pathways [289,290]. However, efficiently and precisely delivering PROTACs to intracranial tumor sites and maximizing their therapeutic efficacy remains a central obstacle on the translational path. To this end,

various delivery systems have been developed. Through functionalized design, these systems aim to achieve targeted brain delivery and controlled release of PROTACs, providing new avenues for overcoming the challenges in treating brain diseases. The following section will focus on reviewing these cutting-edge PROTAC delivery systems for other brain disorders, especially malignant brain tumors.

4.3.1. NPs-based delivery systems

Beyond lipid-based nanocarriers and DNA nanoflowers for NDs, nanocapsules, micelles, and bioinspired nanovesicles have also demonstrated unique advantages as delivery systems for PROTACs to overcome the BBB and chemoresistance in glioma therapy. BRD4 is frequently overexpressed in various diseases, including glioma, hematological malignancies, and inflammatory diseases, where it drives disease progression and therapy resistance by sustaining tumor cell proliferation, survival, and DNA damage repair capacity [291–295]. Given its role as an upstream regulator in core pathogenic pathways and its status as a traditionally 'undruggable' target, BRD4 has become an attractive target for PROTACs in cancer and inflammatory diseases [296]. Accordingly, Guo et al. designed a responsive nanocapsule, MPL(*SS*)P@SIS, to deliver a novel BRD4-targeting PROTAC, SIAIS171142 (SIS), featuring GBM targeting and glutathione (GSH)-responsive release [297]. This nanocapsule is composed of biocompatible PEG-pLys-pPhe polymers, SIS, a GSH-reactive material, and surface modification with 1-methyl-l-tryptophan (MLT), which specifically binds the LAT1 transporter highly expressed on the BBB and GBM cells, facilitating drug transport across the BBB and enrichment within tumor tissue. Following intravenous administration, MPL(*SS*)P@SIS achieved precise drug delivery to the GBM site in an orthotopic GBM mouse model. It disintegrated in the high GSH environment, releasing SIS, which inhibited DNA damage repair via BRD4 degradation, thereby sensitizing tumors to radiotherapy and the chemotherapeutic agent temozolomide (TMZ). Similarly, Yang et al. constructed a micelle system based on substance P peptide modification (SPP-ARV-825) to deliver the BRD4-targeting PROTAC (ARV-825) [14]. Substance P, a neuropeptide, can specifically bind the neurokinin-1 receptor (NK-1R), promoting micelle traversal across the BBB and targeting glioma cells [298]. This micelle system not only inhibited tumor cell proliferation and induced apoptosis through BRD4 degradation but also significantly blocked M2 macrophage polarization, thereby cooperatively modulating the tumor microenvironment and demonstrating marked anti-tumor efficacy in a glioma mouse model. Furthermore, biomimetic nano-delivery systems have also been applied for delivering PROTACs in glioma therapy. Xu et al. developed a biomimetic hybrid PROTAC nanovesicle (M@TP) [299]. Its core involved co-encapsulating a BRD4-targeting PROTAC (Pro) and TMZ within a liposome, which was further camouflaged with the cell membrane of TMZ-resistant glioma cells. This biomimetic design enabled M@TP to recognize and accumulate at the tumor site via homotypic targeting. It subsequently disassembled within GBM cells in the acidic and high GSH environment, releasing the encapsulated Pro. The released Pro effectively blocked the DNA repair pathway in GBM cells by degrading BRD4 protein, thereby resensitizing them to TMZ chemotherapy. In a TMZ-resistant orthotopic GBM mouse model, M@TP significantly suppressed tumor progression and prolonged survival, offering a novel strategy for improving the prognosis of GBM patients.

4.3.2. Prodrug delivery systems

The prodrug strategy is a commonly used drug delivery method. Its current application for PROTAC delivery is evolving beyond traditional prodrugs toward more sophisticated gated activation strategies. The core of this strategy involves masking the active PROTAC molecule during delivery with a cleavable linker, forming a pharmacologically inert prodrug. Activation occurs specifically upon reaching the target lesion area, in response to biochemical signals characteristic of the tumor microenvironment (such as specific enzymes, reactive oxygen species, low pH) or externally applied physical stimuli (such as light), leading to bond cleavage and the subsequent release of the active PROTAC in situ, enabling spatiotemporally controlled and precise protein degradation [300–303]. For instance, Lu et al. developed a tandem-activated PROTAC (TAP) prodrug strategy that enhances the selectivity and specificity of PROTACs in tumors through enzyme-photo dual control [304]. The TAP consists of five sequential units: the PROTAC warhead, a singlet oxygen ($^1O2$)-cleavable moiety, a near-infrared photosensitizer, a Cathepsin B (CatB)-cleavable moiety, and a tumor-homing ligand. CatB is a biomarker enzyme commonly overexpressed in malignant tumors. The PROTAC activity in TAP is initially silenced by both the CatB-responsive group and the photosensitizer. Only after activation of the photosensitizer following CatB cleavage within tumor cells, and subsequent irradiation with a specific wavelength of light to generate $^1O2$, is the linker cleaved, releasing the active PROTAC. Both in vitro and in vivo studies demonstrated that TAP exhibited excellent degradation selectivity under the cooperative action of CatB and near-infrared light, and synergistically inhibited glioma growth when combined with photodynamic therapy. This dual-lock design ensures PROTAC activation specifically within the tumor microenvironment, significantly minimizing off-tumor risks and improving safety, providing a viable strategy for more precise PROTAC therapy.

In summary, delivery systems for PROTACs targeting other brain diseases, particularly glioma, have evolved from simple encapsulation and release formulations to sophisticated, intelligent systems that far exceed traditional delivery concepts. These systems not only strive to cross the BBB but also integrate innovative strategies such as biomimetic targeting, spatiotemporal activation, and microenvironment modulation. They demonstrate significant potential in enhancing tumor targeting, overcoming therapy resistance, and ameliorating immunosuppression, marking a paradigm shift in PROTAC brain delivery research from passive distribution toward active and precise targeting. Furthermore, with the continued convergence of materials science, nanotechnology, and molecular biology, more innovative delivery strategies are expected to emerge, propelling substantial progress for PROTAC technology in treating brain disorders (Table 2).

5. Perspectives and future directions

PROTAC has been explored for treating CNS diseases, particularly NDs, representing a transformative platform for targeting undruggable proteins in CNS disorders and opening novel avenues for therapeutic discovery in previously intractable pathologies [309,310]. Nevertheless, CNS penetrance remains major bottleneck limiting the therapeutic translation of PROTACs in neurological disorders. Rational structural design and advanced delivery systems could effectively optimize CNS delivery of PROTACs. Several strategic paradigms govern BBB-penetrant PROTAC delivery, including CPPs-engineered systems, nanoparticles-based systems, and prodrug-mediated systems. Despite advancements in enhancing PROTACs' brain-targeting capabilities, current research on PROTAC brain delivery systems remains limited, with challenges persisting in delivery efficiency, targeting specificity, and safety profiles.

5.1. Advancing brain-specific PROTAC delivery through innovative platforms

PROTACs are structurally mainly categorized into peptide-based and small molecule-based types. Peptide-based PROTACs exhibit poor membrane permeability, requiring CPPs like R8 for membrane traversal, whereas small molecule-based PROTACs achieve moderate-to-high permeability via passive diffusion [42]. While rational structural modifications can enhance BBB permeability of small molecule PROTACs, critical challenges persist in unclear SAR, complex design paradigms, and suboptimal efficacy. Current delivery systems primarily utilize peptide-based PROTACs, whereas emerging BBB-targeted delivery technologies hold promise for enabling active, targeted brain transport of small molecule PROTACs, thus overcoming limitations of passive

Table 2
Preclinical Studies and Clinical Trials of PROTACs for CNS Disorders.

Drug/Candidate	Target protein	CNS-Relevant Indication/Brain Penetration	E3 ligase	Clinical Phase	Clinical Identifier/ Status
ARV-102	LRRK2	Parkinson's disease; demonstrated CNS penetration and target degradation in CSF	CRBN	Phase 1	Phase 1 ongoing
NX-5948 (bexobrutideg)	BTK	PCNSL / SCNSL cohorts with CNS involvement; reported BBB penetration	CRBN	Phase 1a/1b	NCT05131022
NX-2127 (zelebrudomide)	BTK + IKZF1/3 (dual)	PCNSL (CNS lymphoma involvement)	CRBN	Phase 1a/1b	NCT04830137
C004019 [73]	Tau	Alzheimer's disease	VHL	Preclinical	Preclinical
PT-65 [305]	GSK3	Alzheimer's disease	VHL	Preclinical	Preclinical
2b [306]	α-Synuclein	Parkinson's disease	VHL	Preclinical	Preclinical
PROTAC 2′ [307]	mHTT	Huntington's disease	VHL	Preclinical	Preclinical
XL01126 [32]	LRRK2	Parkinson's disease	CRBN/ VHL	Preclinical	Preclinical
6b [308]	BRD4	Glioblastoma/brain tumor models	CRBN	Preclinical	Preclinical

diffusion mechanisms. The inherent lipophilicity of small molecule PROTACs makes lipid-based nanoparticles (LBPs), including liposomes, solid lipid nanoparticles (SLNs), and lipid nanoparticles (LNPs), particularly suitable for leveraging their lipid compatibility to facilitate brain-targeted PROTAC delivery. Surface engineering of nanocarriers-mediated delivery systems, including exosome- or nanoparticle-based platforms, through functionalization strategies could synergistically improve PROTACs' brain-targeting precision while optimizing their systemic PK profile. Antibody-conjugated nanoparticles targeting BBB receptors (e.g., transferrin receptor/TfR) facilitate receptor-mediated transcytosis through multivalent ligand-receptor interactions; such multiligand nanoformulations may augment TfR clustering-induced endocytic pathways while enhancing transcytotic efficiency across the brain endothelium [311].

Similarly, for peptide-based PROTACs, future research should prioritize developing advanced delivery platforms incorporating multifunctional nanocarriers and structural optimization strategies to synergistically enhance BBB penetration efficiency while improving tissue-specific targeting, thereby addressing current limitations in CNS drug delivery through innovative active targeting modalities. Additionally, a paradigm-shifting dual approach combining optimized drug delivery platforms with intranasal administration could circumvent the BBB through non-invasive routes, leveraging the nasal cavity's olfactory pathway to facilitate direct CNS delivery of PROTAC therapeutics. In conclusion, the progress made in brain delivery technology research in recent years could soon make PROTACs therapies a cornerstone for the treatment of CNS disorders, yet systematic optimization remains imperative to address the unique challenges of emerging structural classes, particularly nucleic acid-based and protein-based PROTACs through innovations in delivery strategies.

5.2. Accelerating BBB-penetrant PROTAC development via AI-driven rational design platforms

Artificial intelligence (AI) has been widely applied to PROTAC design, pharmacodynamic prediction, quantitative structure-property

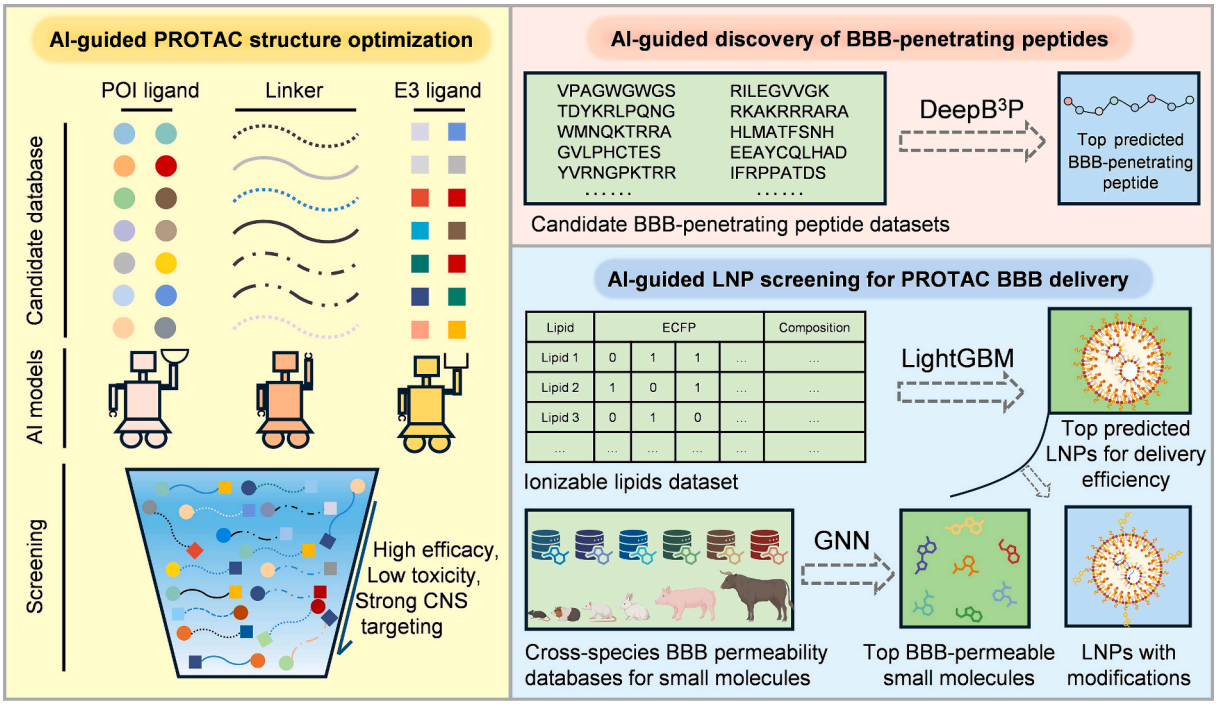


Fig. 5. AI-guided design platforms accelerating BBB-penetrant PROTAC development. Computational methodologies are increasingly used to guide the structural design of PROTACs, predict pharmacodynamic and pharmacokinetic parameters, and identify novel strategies for BBB penetration. Integrating these approaches to optimize BBB-targeted PROTAC architectures and delivery modalities is poised to accelerate the application of PROTACs to central nervous system disorders.

relationships (QSPR) modeling, and delivery-strategy optimization [312,313]. Leveraging artificial intelligence to guide the selection and synthesis of PROTAC candidates with high CNS penetration and favorable pharmacokinetic profiles, or to optimize PROTAC delivery strategies for improved CNS targeting, could accelerate the clinical translation of PROTACs for CNS disorders (Fig. 5).

AI has already advanced the development of potent, target-selective PROTACs. Murakami and colleagues combined chemical language models with reinforcement learning to develop PROTAC-TS, yielding a membrane-permeability predictor ($R^2 = 0.71$) that guided the design of linkers with improved permeability [314]. Li and co-workers proposed DeepPROTAC, a GCN-based framework that predicts degradation potency with notable performance (accuracy = 0.78) [18]. Giulia and collaborators introduced a multi-task graph neural network (MT-GNN) for PROTACs and other TPD molecules, enabling simultaneous estimation of passive permeability, metabolic clearance, cytochrome P450 inhibition, plasma-protein binding, and lipophilicity (Pearson's r = 0.95–0.98) [315]. Integrating these tools suggests a pragmatic pipeline for CNS-directed PROTACs: first, use PROTAC-TS to batch-generate and triage candidates with high membrane permeability; next, apply DeepPROTAC to rerank by predicted degradation potency; finally, enforce multi-property constraints with MT-GNN-based QSPR models, layered with BBB permeability and safety assessments. This funnel would prioritize PROTACs that combine high safety, high BBB penetration, and strong target selectivity, expediting translation for CNS diseases.

Beyond molecular optimization, AI continues to drive discovery in drug-delivery materials, regimen design, and excipient selection-key levers for efficacious CNS formulations [316,317]. Tang et al. introduced DeepB^{3}P, a Transformer-based classifier for BBB-penetrating peptides (AUC = 0.86) and, via explainable-AI analyses, identified amino acids most contributory to BBB translocation-actionable guidance for high-efficiency BBB-crossing strategies [318]. Wang et al. used LightGBM to predict the pKa and delivery efficiency of lipid nanoparticles (LNPs) built from diverse ionizable lipids (accuracy = 0.78), then combined SHAP with a lipid-generation algorithm to nominate high-efficiency LNP formulations [319]. Because conventional LNPs struggle to traverse the BBB, Mor and colleagues trained a GNN to predict small-molecule BBB permeability and, together with biological validation, showed that acetylcholine modification markedly enhances LNP-mediated trans-BBB delivery [320]. Looking ahead, AI can further refine LNP composition and BBB-crossing ligands to improve the CNS targeting of PROTACs.

Future progress will benefit from integrating AI with patient-level multi-omics-genomics, transcriptomics, and proteomics-embedding both PROTAC design and delivery optimization within multimodal deep-learning frameworks to enable individualized CNS therapy [321–323]. However, several challenges remain in advancing AI applications to PROTACs: the opacity of AI predictions requires further experimental validation; the scarcity of pharmacodynamic and pharmacokinetic data for existing PROTACs results in small training sets, which in turn increase the risk of overfitting and poor handling of noisy data; and large models that integrate multi-omics data are costly and energy-intensive to train and infer with, and expensive to retrain [324,325]. Advances in learning algorithms, standardized data-collection pipelines, and the sharing of high-quality multi-omics datasets should help overcome these barriers and accelerate the realization of precise, CNS-targeted PROTAC therapies.

5.3. Emerging therapeutic potential of novel TPD technology

Conventional TPD approaches primarily include PROTACs and molecular glues, which differ in their mechanisms of recruiting E3 ubiquitin ligases to induce target protein degradation [326]. Current extensions of TPD platforms are primarily based on a series of novel heterobifunctional chimeras derived from PROTAC paradigm. These next-generation degraders enhance the selectivity and precision of TPD across both temporal and spatial dimensions, ultimately improving therapeutic outcomes [327].

5.3.1. Novel heterobifunctional chimeras

The ubiquitin-proteasome system and the lysosomal proteolytic pathway represent the two primary protein degradation mechanisms in human cells. Lysosome-Targeting Chimera (LYTAC) harnesses the lysosomal degradation pathway to enable targeted degradation of extracellular and membrane proteins, thereby expanding the therapeutic scope of TPD technology as an important complement to PROTAC [328]. Structurally, LYTAC features a glycopeptide moiety at one end that engages the cell surface transmembrane receptor CI-M6PR, while the other end is conjugated to an antibody or small molecule ligand that specifically binds the target protein. This configuration enables LYTAC to direct extracellular proteins to cell surface receptors, facilitating their internalization and subsequent degradation through the endosomal-lysosomal pathway. By incorporating APOE4-specific antibodies, LYTAC technology achieves efficient clearance of APOE4, a secreted apolipoprotein, contributes to AD pathogenesis, demonstrating its significant potential for treating central nervous system disorders [329]. In addition to broadening the range of degradable proteins across spatial dimensions, TPD technology is increasingly applied to modulate specific intracellular biological pathways. Autophagy, a critical cellular clearance mechanism, eliminates protein aggregates and superfluous or impaired organelles through the lysosomal proteolysis pathway [330]. It plays a fundamental role in maintaining cellular homeostasis, and its dysfunction is strongly associated with the pathogenesis of several neurodegenerative disorders [331,332]. In 2019, Hirokazu Arimoto and his team identified S-guanylation as a universal signal triggering the autophagic degradation of proteins and organelles [333]. Building on this discovery, they introduced the concept of Autophagy-Targeting Chimera (AUTAC). An AUTAC molecule is composed of three elements: a target protein ligand, a linker, and an FBnG moiety—an S-guanylation-based degradation tag. In their study, an AUTAC designed to bind the mitochondrial membrane translocator protein (TSPO) selectively targeted damaged mitochondria for degradation, enhanced mitophagy, and ultimately improved mitochondrial function [333].

Post-translational modifications (PTMs) substantially enhance proteomic diversity and profoundly expand the functional repertoire of proteins. Precise regulation of specific biological functions of target proteins cannot be achieved through total protein degradation but requires accurate manipulation of their PTM status. Among various PTMs, phosphorylation stands as one of the most biologically significant. It not only directly regulates critical cellular processes but also engages in dynamic crosstalk and competition with other PTMs on the same protein, enabling sophisticated functional fine-tuning. The hyperphosphorylation of Tau protein represents a central pathological mechanism in AD. To address this, the Crews laboratory developed Phosphorylation-Targeting Chimeras (PhosTACs) [334]. These heterobifunctional molecules are designed to recruit phosphatases to specific target proteins, thereby inducing precise dephosphorylation. In their proof-of-concept study, the team employed PI-2620, an established PET Tau tracer, as the target-binding moiety to direct PhosTACs specifically to Tau. However, a current limitation remains the recruitment of phosphatase PP2A, which still depends on engineered fusion tags due to the scarcity of specific small-molecule ligands. Despite this constraint, their PhosTAC platform successfully reduced phosphorylation at multiple Tau epitopes, including the pathologically relevant pThr231 and pThr181 sites [335]. Looking forward, the discovery of next-generation Tau-specific binders and authentic small-molecule ligands for endogenous phosphatases may unlock the full therapeutic potential of PhosTAC technology. This advancement could position it as a promising strategy for AD and other disorders driven by aberrant phosphorylation.

Similarly, these emerging TPD technologies beyond PROTACs require BBB penetration for clinical translation. Cutting-edge BBB delivery systems, such as nanocarriers and cell membrane based

biomimetic vehicles, need to be further explored to enable CNS-targeted transport of next-generation degraders, advancing novel therapeutics for CNS disorders.

5.3.2. Molecular glues

Molecular glues are promising TPD platforms addition to the heterobifunctional molecules. PROTACs typically adopt a bivalent architecture composed of a target-binding ligand, an E3 ligase-recruiting ligand, and a linker connecting the two. This three-component design confers a high degree of modularity and programmability, but it also generally results in relatively high molecular weight. In contrast, molecular glues are usually monovalent small molecules that induce or stabilize a protein-protein interaction between an E3 ligase and a target protein, effectively gluing the two proteins together without the need for a linker-driven scaffold [326,336]. This mechanistic distinction translates into meaningful differences for CNS drug development. From a delivery standpoint, PROTACs often reside in beyond-rule-of-five chemical space, with high molecular weight and polarity that collectively limit passive permeability and can exacerbate BBB efflux liability and intracellular access constraints. Molecular glues, by virtue of their smaller size and often more drug-like physicochemical profiles, may offer advantages in solubility, oral exposure, and BBB penetration, potentially improving the probability that adequate free concentrations can be achieved in the brain and within neural cells [337]. However, molecular glues also face distinct limitations, including less standardized design rules, context-dependent SAR and ternary complex kinetics, and the risk of unanticipated substrate recruitment and off-target degradation-considerations that are especially critical for CNS safety [68]. Therefore, while both modalities share common barriers, the relative weight of these constraints differs: PROTACs are often dominated by physicochemical and intracellular delivery limitations, whereas molecular glues may shift the bottleneck toward target/E3 compatibility, selectivity control, and safety window optimization. A balanced discussion of both modalities is essential for rational selection of TPD strategies in CNS indications.

6. Conclusion

This review systematically examines the delivery challenges and recent advances in applying PROTAC technology as a novel therapeutic strategy for brain disorders. By targeting previously “undruggable” pathogenic proteins, PROTAC technology offers revolutionary therapeutic prospects for CNS conditions, including NDs. However, the clinical translation of this technology faces significant hurdles, primarily stemming from the inherent high molecular weight and polar nature of PROTACs, coupled with the stringent restrictive properties of the BBB. In this context, this article comprehensively summarizes recent progress in BBB-penetrating drug delivery and existing strategies for transporting PROTACs into the brain. It emphasizes that rational molecular optimization combined with advanced delivery systems holds considerable promise for translating the therapeutic potential of PROTACs into clinical reality. Looking forward, sustained progress will depend on the deep integration of multidisciplinary innovation, spanning AI-driven molecular design, adaptive delivery nanoplatforms, and the discovery of novel degradation modalities. Through such convergence, the long-standing challenge of brain-specific drug delivery may finally be resolved, redefining therapeutic intervention in neurodegenerative disease.

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Declaration of competing interest

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

Data availability

No data was used for the research described in the article.

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