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Review Article

Translational Strategies for Blood-Brain Barrier Penetration and Targeted Central Nervous System Drug Delivery

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Abstract

The blood-brain barrier (BBB) is a highly selective semi-permeable interface that maintains central nervous system (CNS) homeostasis by tightly regulating the passage of substances from systemic circulation into the brain. While essential for neuroprotection, this barrier presents the foremost challenge in neuropharmacology, effectively excluding the vast majority of small-molecule drugs and nearly all large-molecule biopharmaceuticals from reaching therapeutic targets within the CNS. Diseases such as glioblastoma, Alzheimer's disease, Parkinson's disease, and a broad spectrum of neurological disorders therefore remain difficult to treat despite considerable advances in drug development. This review aims to provide a comprehensive and critically evaluated combination of current and emerging strategies for CNS drug delivery, mapping the translational landscape from experimental methodologies to clinical application, with particular attention to advances reported in 2025 and 2026. The review systematically examines both non-invasive and invasive approaches to overcoming the BBB. Non-invasive strategies include carrier-mediated transport, receptor-mediated transcytosis (RMT), peptide-based delivery systems incorporating cell-penetrating and receptor-targeting peptides, and nanotechnology-based therapeutics such as lipid nanoparticles, polymeric nanocarriers, and exosome-based platforms. Among invasive physical disruption methods, microbubble-enhanced focused ultrasound (MB-FUS) and convection-enhanced delivery are evaluated for their clinical utility and safety profiles. The integration of peptide-based systems with nanocarriers is highlighted as a particularly modular and scalable strategy for targeted CNS pharmacotherapy. Clinical trial data from 2025 and 2026 are incorporated to contextualize these strategies within real-world therapeutic outcomes, including demonstrated survival benefits in glioblastoma patients and accelerated amyloid clearance in Alzheimer's disease. The review further discusses the emerging role of artificial intelligence in enabling precision neuro-nanomedicine, from target identification to personalized dosing optimization, alongside the evolving regulatory landscape governing CNS drug delivery technologies. This review provides a forward-looking roadmap for the clinical translation of targeted CNS pharmacotherapy, underscoring the necessity of interdisciplinary collaboration among neuroscience, nanotechnology, neuropharmacology, and regulatory science to overcome the persistent challenge posed by the blood-brain barrier (BBB).

Keywords

Blood-Brain Barrier (BBB), CNS Drug Delivery, Receptor-Mediated Transcytosis (RMT), Nanotechnology-Based Therapeutics, Focused Ultrasound (MB-FUS), Neuropharmacology

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1. Introduction

1.1. The Evolutionary Safeguard and the Clinical Imperative

The architectural complexity of the human brain is governed by a sophisticated homeostatic environment maintained by the blood-brain barrier (BBB) [1, 2]. This highly selective semi-permeable interface is a vital evolutionary adaptation that preserves the neural milieu by excluding pathogens, neurotoxic agents, and systemic fluctuations in ionic concentration. However, the same physiological mechanisms that protect the brain represent the primary obstacle in modern neuropharmacology [1, 3]. Current estimates indicate that the BBB effectively excludes nearly 100% of large-molecule biopharmaceuticals and approximately 98% of small-molecule compounds, resulting in the clinical failure of numerous promising therapies for glioblastoma multiforme (GBM), Alzheimer's disease (AD), Parkinson's disease (PD), and rare lysosomal storage disorders [1, 3, 4]. As neurological disorders have become the leading cause of disability worldwide - affecting over three billion individuals by 2024—the challenge of drug delivery to the central nervous system (CNS) has transitioned from a structural problem to a global health priority.

The contemporary paradigm in CNS therapeutics has shifted from attempting to physically "break" the barrier - a strategy prone to inducing vasogenic edema and neuroinflammation - to a more nuanced approach of "negotiating" with its endogenous transport systems [2, 3]. This transition is underpinned by advancements in nanotechnology, molecular biology, and transcranial physical disruption. The years 2025 and 2026 have marked a pivotal era in this field, characterized by the reporting of the first-ever survival benefits in GBM via focused ultrasound and the clinical approval of biologics engineered for receptor-mediated transcytosis [5-7]. This report provides an exhaustive synthesis of the molecular landscape of the BBB, evaluates non-invasive physiological strategies alongside invasive physical disruption techniques, and integrates real-time clinical trial data representing the current state of targeted CNS pharmacotherapy [4].

1.2. Physiological and Molecular Landscape of the Blood-Brain Barrier

The BBB is the functional core of the neurovascular unit (NVU), a dynamic multicellular complex that integrates the microvascular endothelium with mural cells and glial components [2, 8]. The integrity of this barrier arises from synergistic interactions between brain microvascular endothelial cells (BMECs), pericytes, astrocytes, and the specialized basement membrane [2, 8, 9].

1.2.1. Microvascular Endothelial Cells and Junctional Complexes

BMECs are the primary physical partition of the BBB. Unlike peripheral endothelial cells, BMECs lack fenestrations, demonstrate a sparse rate of pinocytic vesicular transport, and possess a high concentration of mitochondria to support active transport mechanisms [1, 2]. The defining feature of these cells is the presence of elaborate tight junction (TJ) and adherens junction (AJ) complexes that seal the paracellular space, obliterating the interendothelial cleft [2, 8]. Tight junctions consist of claudins (particularly claudin-5), occludin, and junctional adhesion molecules (JAMs), which are linked to the actin cytoskeleton via zonula occludens (ZO) scaffolding proteins [2, 8]. The resulting transendothelial electrical resistance (TEER) is exceptionally high, restricting the passage of polar solutes and ions [1, 10].

Table 1. *Tight Junction and Adherens Junction Protein Classes at the BBB.*

Protein Class	Representative Molecules	Structural and Functional Role	Pathological Significance
Claudins	Claudin-5, Claudin-3, Claudin-12	Forms the primary paracellular seal; restricts small ions and polar solutes.	Loss leads to vasogenic edema and "leaky" tumor vasculature in stroke and hypoxia.
Occludin	65-kDa integral protein	Regulates electrical resistance (TEER) and junctional stability.	Downregulated in neuroinflammation; correlates with barrier breakdown in Alzheimer's.
JAMs	JAM-1, JAM-2, JAM-3	Involved in leukocyte extravasation and cell polarity.	Mediates inflammatory cell infiltration in multiple sclerosis.
Scaffolding	ZO-1, ZO-2, ZO-3	Contains PDZ domains; links transmembrane proteins to the actin cytoskeleton.	Disruption compromises the physical scaffolding of the barrier.
Adherens	VE-Cadherin, Catenins	Facilitates initial cell-cell adhesion and stabilizes junctional assembly.	Essential for pericyte recruitment and vascular development.

1.2.2. Mural Cells and Molecular Signaling Pathways

Pericytes (PCs) are mural cells embedded within the capillary basement membrane. They are essential for regulating angiogenesis, controlling capillary diameter, and inducing the expression of TJ proteins during development [9, 11, 12]. Pericyte-deficient models exhibit increased BBB permeability and a breakdown in bulk flow transcytosis regulation [13]. Astrocytes contribute to the BBB through their perivascular endfeet, which ensheathe approximately 99% of the microvasculature. While astrocytes do not provide a physical barrier in the mammalian brain, they are critical for maintaining the TJ seal through the secretion of signaling molecules like glial cell line-derived neurotrophic factor (GDNF) and Src-suppressed C-kinase substrate (SSeCKS) [2, 8, 10].

Recent molecular signaling reviews highlight the importance of the PDGF-BB/PDGFR-β pathway between endothelial cells and pericytes for maintaining microvascular stability [12]. Additionally, astrocytes secrete Apolipoprotein E (ApoE3), which binds to low-density lipoprotein receptor-related protein 1 (LRP1) on pericytes, suppressing the pro-inflammatory CypA-NF-κB-MMP-9 pathway and preventing the degradation of junctional proteins [12, 14]. In contrast, the ApoE4 variant lacks this protective effect, providing a mechanistic link between human genetic risk factors and BBB dysfunction in Alzheimer's disease [14].

1.3. Biochemical Defense Mechanisms: Efflux and Metabolic Barriers

The BBB acts not only as a physical wall but also as a biochemical shield. Therapeutics managing to pass paracellular tight junctions or enter endothelial cytoplasm are often subject to active expulsion or enzymatic deactivation [4, 15].

1.3.1. ABC Transporters and P-glycoprotein

The ATP-binding cassette (ABC) transporters are the primary gatekeepers for small molecules [15]. The most extensively characterized member is P-glycoprotein (P-gp/ABCB1), which utilizes ATP hydrolysis to expel over 200 chemically diverse substrates—including many chemotherapeutics and antiepileptics—back into the blood [4, 15]. The mechanism follows a "vacuum-cleaner" model where substrates entering the lipid bilayer are captured by transmembrane domains (TMDs) and ejected upon the binding of ATP to nucleotide-binding domains (NBDs), which induces a global conformational shift [15].

1.3.2. Metabolic Deactivation

The BBB houses enzymes capable of inactivating drugs, including cytochrome P450 (CYP450), monoamine oxidases (MAO), and diverse peptidases. This metabolic component chemically alters therapeutics, making them more polar and increasing their susceptibility to ABC transporters [4, 15]. Furthermore, the accumulation of certain nanoparticles, such as iron oxide nanoparticles (IONPs), can fuel the Fenton reaction, producing hydroxyl radicals that induce ferroptosis and neurodegeneration, highlighting the need for biocompatible surface functionalization in nanotechnology platforms [16].

1.4. Endogenous Transport Systems as Portals for Drug Delivery

Strategies to "negotiate" with the BBB exploit natural pathways: carrier-mediated transport (CMT), receptor-mediated transcytosis (RMT), and adsorptive-mediated transcytosis (AMT) [3, 6, 17].

1.4.1. Carrier-Mediated Transport (CMT)

CMT utilizes Solute Carrier (SLC) proteins to transport small-molecule nutrients along their concentration gradient [15]. GLUT1 (SLC2A1), accounting for over 90% of BBB glucose transport, has been targeted using glucose-drug conjugates like V-TDS-G, which achieved 5.7 times higher brain concentration than unmodified drugs [4, 15]. Similarly, LAT1 (SLC7A5) transports essential amino acids; prodrugs of ketoprofen and nipecotic acid linked to amino acid fragments have shown improved penetration in clinical models [4, 15].

1.4.2. Receptor-Mediated Transcytosis (RMT)

RMT is a highly selective mechanism where a ligand binds to its receptor on the luminal side of the endothelial cell, triggering endocytosis and trafficking to the abluminal side [6, 17]. The transferrin receptor (TfR1) is the most studied RMT target due to its high expression on BMECs [6, 17, 18]. However, early RMT strategies were hindered by high-affinity bivalent antibodies that caused receptor clustering and lysosomal degradation rather than successful transcytosis [6, 17].

Optimization of RMT involves a delicate balance of affinity and valency. Roche's trontinemab (using the BrainShuttle technology) employs a monovalent, low-affinity Fab fragment to bind TfR [18-20]. This allows the antibody to detach from the receptor upon reaching the abluminal side, preventing sequestration within the endothelial cell [20, 21]. In 2025, Roche reported that trontinemab cleared plaque in deep-brain regions not touched by conventional antibodies, with 91% of participants becoming amyloid-negative within 28 weeks [20, 21].

2. Nanotechnology-Based Drug Delivery Platforms

Nanocarriers protect therapeutics from degradation and provide navigation pathways across the BBB. Successful delivery generally requires particle sizes under 150 nm and surface modifications to evade the reticuloendothelial system [3, 16].

2.1. Lipid-Based Nanoparticles (LNPs) and Ionizable Lipids

LNPs, including liposomes and solid lipid nanoparticles (SLNs), are highly biocompatible. The inclusion of ionizable lipids is a critical advancement; these lipids remain neutral at physiological pH but become positively charged at low pH within the endosome. This pH-dependent charging triggers the release of nucleic acid cargo into the cytoplasm [16, 22]. In April 2026, Galmed Pharmaceuticals announced a breakthrough brain-penetrating formulation of its drug Aramchol, encapsulated in LNPs designed to cross the BBB and target stearoyl-CoA desaturase 1 (SCD1) to reduce α-synuclein aggregation in Parkinson's disease [23-26].

2.2. Endosomal Escape: The VBC Mechanism

A critical bottleneck in LNP delivery is endosomal escape, as only 1-3% of internalized RNA typically reaches the cytosol [22, 27]. Emerging research in 2025 suggests that LNPs escape through a "vesicle budding-and-collapse" (VBC) mechanism rather than the traditional "proton sponge" model [22, 27, 28]. This mechanism proposes that endosomal escape triggers the formation of insoluble lipid/nucleic acid aggregates within the cytoplasm, whose slow dissolution acts as a secondary rate-limiting step for functional drug delivery [22].

2.3. Physical and Invasive Methodologies for BBB Disruption

When non-invasive strategies are insufficient, physical opening of the barrier or direct bypassing is required to achieve therapeutic concentrations [28, 30].

2.3.1. Microbubble-Enhanced Focused Ultrasound (MB-FUS)

MB-FUS provides localized, transient BBB opening by applying transcranial low-intensity ultrasound to intravenously injected gas-filled microbubbles. The periodic pulsation of these bubbles (stable cavitation) mechanically stretches the BMECs, temporarily opening tight junctions for a 4–6-hour window [28-30].

In 2025, the results of the landmark BT008NA trial demonstrated the first survival benefit in GBM patients receiving MB-FUS plus temozolomide. The trial showed a median overall survival (OS) of 31.3 months compared to 19 months in the control group—a 40% increase [29-31]. Furthermore, the study introduced "sono-liquid biopsy," utilizing MB-FUS to increase the clearance of neurotoxins and enhance the shedding of brain tumor markers (cfDNA) into the bloodstream for non-invasive monitoring [29, 31].

2.3.2. Convection-Enhanced Delivery (CED)

CED uses pressure gradients to bypass the BBB, infusing drugs directly into the brain parenchyma. Its efficacy has historically been limited by the anisotropic nature of white matter, where nerve bundles cause unpredictable drug distribution [32-34]. However, advanced catheters like the SmartFlow cannula, which received De Novo FDA authorization in late 2024, utilize a stepped distal tip to minimize backflow and enable precise delivery of gene therapies like KEBILIDI for AADC deficiency [34]. In March 2025, the ReSPECT-GBM trial reported that Rhenium-186 nanoliposomes delivered via CED more than doubled median survival for recurrent glioma patients who received doses greater than 100 Gy [35].

3. Peptide-Mediated BBB Translocation Strategies

Peptide-based delivery systems have emerged as a versatile and highly tunable approach for facilitating the transport of therapeutic agents across the blood-brain barrier (BBB). These systems exploit short amino acid sequences capable of interacting with endothelial membranes or endogenous transport pathways, thereby enabling efficient translocation into the central nervous system (CNS). Compared to large biologics or synthetic nanocarriers, peptides offer distinct advantages including low immunogenicity, structural flexibility, ease of synthesis, and amenability to chemical modification.

One of the most extensively studied classes is cell-penetrating peptides (CPPs), such as the trans-activator of transcription (TAT) peptide derived from HIV-1 and penetratin. CPPs facilitate energy-independent translocation or endocytosis-mediated uptake by interacting with negatively charged components of the endothelial cell membrane, including glycosaminoglycans and phospholipids [36]. These peptides can be conjugated to a wide range of cargoes—including small molecules, proteins, nucleic acids, and nanoparticles-thereby enhancing intracellular delivery within brain endothelial cells and subsequent parenchymal distribution.

In parallel, receptor-targeting peptides, often referred to as BBB shuttle peptides, are designed to exploit endogenous receptor-mediated transcytosis (RMT) pathways. Notable examples include Angiopep-2, which targets the low-density lipoprotein receptor-related protein 1 (LRP1), and apolipoprotein E (ApoE)-mimetic peptides that similarly engage lipid transport systems [37]. These peptides demonstrate high specificity and transcytosis efficiency, enabling targeted delivery to neurons and glial cells while minimizing off-target distribution. Importantly, peptide affinity and valency can be fine-tuned to avoid receptor saturation and lysosomal degradation—challenges also observed in antibody-based RMT systems.

Recent advances have focused on peptide-functionalized nanocarriers, which integrate the advantages of nanotechnology with biological targeting specificity [38]. Surface conjugation of peptides onto lipid nanoparticles (LNPs), polymeric

nanoparticles, or exosomes enhances BBB permeability, promotes cellular uptake, and improves endosomal escape. Such hybrid systems are particularly promising for nucleic acid delivery, where peptide ligands facilitate both BBB traversal and cytosolic release, addressing key bottlenecks identified in nanomedicine platforms.

Despite these advantages, several challenges remain. Peptides are susceptible to proteolytic degradation in systemic circulation and may exhibit rapid renal clearance, necessitating stabilization strategies such as cyclization, D-amino acid substitution, or PEGylation [39]. Furthermore, large-scale manufacturing and regulatory standardization of peptide-drug conjugates require further optimization.

Overall, peptide-mediated delivery represents a critical convergence of molecular biology and nanotechnology, offering a modular and scalable platform for next-generation CNS therapeutics. When integrated with existing strategies such as receptor-mediated transcytosis and lipid nanoparticle systems, peptide-based approaches have the potential to significantly enhance the precision, efficiency, and clinical translatability of BBB-targeted pharmacotherapy.

4. Clinical Breakthroughs and Regulatory Milestones (2024-2026)

The years 2025 and 2026 have represented a paradigm shift in the regulatory acceptance of CNS delivery technologies [4, 40].

4.1. FDA Approval of AVLAYAH (Tividenofusp Alfa)

On March 25, 2026, the FDA granted accelerated approval to AVLAYAH (tividenofusp alfa-eknm) for the treatment of neurologic manifestations of Hunter syndrome (MPS II) in pediatric patients. This is the first product approved specifically to address neurologic complications in this rare disorder [7, 8, 41, 42]. AVLAYAH utilizes Denali Therapeutics' "Transport Vehicle" platform, which targets the transferrin receptor (TfR) to ferry the iduronate-2-sulfatase enzyme across the BBB [42]. The approval was based on a 91% average reduction in CSF heparan sulfate, a surrogate biomarker of clinical benefit [7].

Table 2. *Key Clinical Trials and Regulatory Milestones (2025-2026).*

Trial / Drug Name	Phase	Technology	Primary Findings / Status (2025-2026)	References
BT008NA	1/2	MB-FUS + TMZ	40% OS increase (31.3 vs 19 months) in GBM; Dec 2025 report.	[29-31]
TRONTIER 1 & 2	3	Trontinemab	91% PET-negative clearance in AD; Phase 3 started Sept 2025.	[19-21]
AVLAYAH	1/2	RMT (TfR)	91% CSF HS reduction; FDA Accelerated Approval March 2026.	[7, 41, 42]
LIMITLESS RCT	RCT	MB-FUS + Pembrolizumab	Ongoing; Evaluating safety/efficacy in NSCLC brain metastases.	[43]
ReSPECT-GBM	1	CED + 186Re-RNL	Median OS 17 months at doses >100 Gy in recurrent glioma.	[35]
Aramchol-LNP	1b/2	LNP + SCD1 Inhibitor	Planned for H2 2026 for Parkinson's; April 2026 announcement.	[23-25]

4.2. Emerging Research Tools and Future Horizons

Translational success is being accelerated by AI-driven design and high-fidelity human modeling [44].

4.2.1. iPSC-Derived 3D BBB-on-a-Chip

Traditional animal models fail to capture human-specific genetic risk factors, such as the FOXF2 mutation linked to small vessel disease [9, 41]. In December 2025, a study in Nature Neuroscience presented a fully human iPSC-derived 3D BBB model. This model forms perfusable vessel-like tubes with functional markers and was used to test the delivery of LNPs carrying Foxf2 mRNA, which successfully rescued barrier impairment [9, 11, 41, 42]. Such platforms provide a scalable testbed for predicting drug transport and studying neurovascular disease mechanisms [9].

4.2.2. AI-Driven Precision Neuro-Nanomedicine

Machine learning models are now used to predict BBB permeability by analyzing molecular descriptors like total polar surface area and partition coefficients [44]. Deep neural networks (DNNs) have achieved AUCs of 0.98 on permeability

benchmark sets [44]. Furthermore, AI-guided ligand screening is optimizing affinity to prevent receptor saturation, a strategy employed in the design of the latest generation of RMT "shuttles" and the Aramchol-LNP formulation [23, 44].

5. Discussion: Translational Hurdles and Market Dynamics

The evidence synthesized in this review reflects a defining transition in CNS pharmacotherapy — from treating the BBB as an absolute pharmacological boundary to recognizing it as a navigable biological interface amenable to rational therapeutic engagement. However, this transition is accompanied by unresolved mechanistic, biological, and systemic challenges that must be addressed before these strategies achieve their full clinical potential.

A central tension persists between the efficacy of barrier permeabilization and the preservation of CNS homeostasis. MB-FUS achieves targeted, transient tight junction opening but carries residual risks of neuroinflammatory sequelae, including microglial activation and pro-inflammatory cytokine release, even under stable cavitation conditions. Inertial cavitation, if inadequately controlled, may induce microhemorrhage, necessitating real-time acoustic monitoring. CED bypasses the barrier entirely but remains constrained by the anisotropic microstructure of white matter, which produces unpredictable distribution volumes that deviate substantially from idealized convection models. Overcoming this limitation demands integration of patient-specific tractography with MRI-guided, real-time infusion control.

Non-invasive RMT platforms have produced the most mechanistically elegant solutions to date. The critical insight that monovalent, reduced-affinity TfR1 binding prevents receptor clustering and lysosomal sequestration - thereby enabling genuine transcytosis rather than intracellular entrapment - represents a fundamental refinement over earlier bivalent antibody strategies [45]. This principle of affinity-valency optimization extends broadly to peptide-functionalized nanocarrier systems, where receptor saturation at the luminal BBB surface remains a clinically relevant bottleneck.

Endosomal escape constitutes a shared rate-limiting step across LNP, peptide-nanocarrier, and hybrid delivery platforms. The emerging VBC mechanistic model suggests that cytoplasmic aggregate dissolution, rather than endosomal membrane disruption alone, governs the kinetics of functional RNA release - a finding with direct implications for rational ionizable lipid formulation design. Complementarily, the PEG dilemma - wherein surface shielding necessary for RES evasion simultaneously impairs cellular uptake - demands stimuli-responsive, cleavable linker strategies that reconcile systemic stability with intracellular bioavailability [46].

Peptide-based delivery systems offer structural versatility and biological specificity but face persistent challenges in proteolytic stability, peripheral non-specificity, and GMP-scalable manufacturing. Stabilization through cyclization, D-amino acid substitution, or retro-inverso isomerization must be balanced against potential alterations in receptor recognition and membrane interaction kinetics.

AI-driven permeability prediction models, while achieving high benchmark accuracy, are predominantly trained on passive diffusion datasets and therefore fail to capture the contributions of active RMT, efflux transporter affinity, and disease-state-dependent barrier remodeling. Next-generation predictive frameworks must integrate multi-omic transport data and patient-specific BBB transcriptomic signatures to achieve genuine pharmacokinetic utility [39].

Finally, the regulatory classification of device-drug and device-biologic combination products remains structurally misaligned with the complexity of emerging CNS delivery platforms. The harmonization of international regulatory standards, development of validated functional CNS biomarkers beyond existing surrogate endpoints, and construction of adaptive HTA frameworks capable of capturing long-term neurological benefit are institutional prerequisites for the sustainable clinical scaling of these technologies.

6. Conclusion

The period spanning 2025 and 2026 represents a watershed in the clinical translation of blood-brain barrier traversal technologies, characterized by the transition from mechanistic proof-of-concept to regulatory approval and validated survival benefit. The first-ever demonstration of a significant overall survival advantage in glioblastoma multiforme through MB-FUS-augmented chemotherapy (BT008NA trial), the near-complete amyloid clearance achieved by the monovalent TfR1-targeting biologic trontinemab in Alzheimer's disease, and the FDA accelerated approval of AVLAYAH - the first RMT-enabled enzyme replacement therapy targeting neurological manifestations of MPS II - collectively mark an inflection point that the field has been approaching for three decades [18].

This review has demonstrated that no single delivery modality is sufficient across the full spectrum of CNS diseases. Rather, the therapeutic landscape is converging toward multimodal and combinatorial approaches in which the complementary strengths of individual strategies are strategically integrated. RMT-functionalized nanocarriers can traverse the intact BBB to deliver nucleic acid therapeutics with high specificity; MB-FUS can transiently open the barrier in focal disease regions to permit the entry of macromolecular payloads that would otherwise be excluded; CED can bypass the barrier entirely for direct parenchymal delivery in diseases where systemic pharmacokinetics are inherently unfavorable; and peptide-based shuttle systems provide a modular, chemically versatile layer of biological targeting that can be grafted onto virtually any nanoparticle or biologic scaffold. The emerging in-

tegration of these platforms with AI-guided ligand optimization, real-time MRI monitoring, and human iPSC-derived BBB models is beginning to close the translational gap between preclinical promise and clinical reality [9].

Nevertheless, several critical unresolved challenges must be addressed before these technologies achieve their full therapeutic potential. The endosomal escape efficiency of LNP platforms remains critically low, with most of the internalized cargo subject to lysosomal degradation rather than cytosolic release. Mechanistic clarity on the VBC model of endosomal escape must be translated into rational formulation design principles that maximize functional payload delivery. The proteolytic instability and non-specificity of cell-penetrating peptides demand chemical engineering solutions — including cyclization, D-amino acid substitution, and stimuli-responsive conjugation — that preserve membrane interaction capacity while conferring selectivity and plasma stability. The PEG dilemma in nanoparticle design, wherein surface shielding necessary for RES evasion impairs cellular uptake and endosomal escape, requires smart, responsive linker chemistries that are both manufacturable at scale and regulatorily acceptable.

From a clinical translation perspective, the development of validated functional biomarkers for CNS drug delivery efficacy is urgently required. The field currently relies on surrogate endpoints - CSF protein levels, amyloid PET burden, neurofilament light chain — that, while biologically informative, do not fully capture the functional neurological benefit that patients and regulatory agencies ultimately demand. Longitudinal, multi-site natural history studies integrating quantitative imaging, multiomic CSF proteomics, and digital cognitive assessments will be essential to establish the correlation between delivery-mediated biomarker changes and durable clinical outcomes.

Regulatory architecture governing combination products must evolve in concert with science. The harmonization of international regulatory standards for device-drug and device-biologic combinations, the development of adaptive trial designs capable of efficiently evaluating multimodal delivery strategies, and the establishment of HTA frameworks that appropriately value long-term neurological benefit in cost-effectiveness analyses are institutional prerequisites for the sustainable clinical scaling of these technologies.

Looking forward, the most transformative developments in the field are likely to arise from the convergence of three vectors: first, the maturation of human iPSC-derived BBB organoid and microfluidic models as high-fidelity preclinical screening platforms capable of capturing patient-specific genetic risk factors and disease-stage-dependent barrier alterations; second, the development of next-generation AI models trained on multi-dimensional transport data - integrating passive permeability, active RMT kinetics, efflux transporter affinity, and plasma protein binding - to enable genuinely predictive CNS pharmacokinetic modeling; and third, the clinical validation of sono-liquid biopsy as a non-invasive neuro-oncological monitoring tool, leveraging MB-FUS-enhanced cfDNA shedding to provide real-time tumor genomic information without surgical intervention [47].

In summation, the blood-brain barrier, long regarded as the defining limitation of clinical neuropharmacology, is being systematically recharacterized as a targetable biological interface. The strategies reviewed herein - spanning carrier-mediated and receptor-mediated transcytosis, advanced nanotechnology platforms, peptide-based shuttle systems, focused ultrasound, and convection-enhanced delivery - are no longer theoretical constructs but clinically validated, regulatory-approved, or late-stage investigational tools. The imperative now is integration: building delivery architectures that combine molecular precision with physical accessibility, guided by artificial intelligence, validated in human-specific biological models, and evaluated through adaptive, biomarker-enriched clinical trials. The era of rational, targeted CNS pharmacotherapy has demonstrably begun, and the biological complexity of the blood-brain barrier is, for the first time, being matched by the sophistication of the tools designed to navigate it.

Abbreviations

AADC	Aromatic L-Amino Acid Decarboxylase
ABC	ATP-Binding Cassette
AMT	Adsorptive-Mediated Transcytosis
BBB	Blood-Brain Barrier
BMECs	Brain Microvascular Endothelial Cells
CED	Convection-Enhanced Delivery
CMT	Carrier-Mediated Transport
CNS	Central Nervous System
CYP450	Cytochrome P450
GBM	Glioblastoma Multiforme
GDNF	Glial Cell Line-Derived Neurotrophic Factor
IONPs	Iron Oxide Nanoparticles
LAT1	Large Neutral Amino Acid Transporter 1 (SLC7A5)
LNPs	Lipid Nanoparticles
PDGF-BB	Platelet-Derived Growth Factor BB
PDGFR-β	Platelet-Derived Growth Factor Receptor Beta
PET	Positron Emission Tomography
SCD1	Stearoyl-CoA Desaturase 1
SLNs	Solid Lipid Nanoparticles
TMDs	Transmembrane Domains
VBC	Vesicle Budding-and-Collapse

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Author Contributions

Arunima Ghosh: Conceptualization, Formal Analysis, Investigation, Resources, Writing – original draft

Sourav Dutta: Data curation, Methodology, Supervision, Validation, Writing – review & editing

Conflicts of Interest

The authors declare no conflicts of interest.

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