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Overcoming Biological Barriers: A Review of Nanomedicine Strategies for Crossing the Blood-brain Barrier in Neuro-oncology

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Abstract

The formidable challenge of crossing the blood-brain barrier (BBB) remains a critical impediment to effective drug delivery for neuro-oncological diseases. This protective mechanism severely restricts the passage of therapeutic agents, necessitating innovative strategies to achieve sufficient drug concentrations within the brain. This review comprehensively examines the latest advancements in nanomedicine designed to overcome this significant biological obstacle. We explore the fundamental structure and function of the BBB to establish a foundation for understanding nanocarrier design principles. The review details key nanomedicine approaches, including the use of cell-penetrating peptides, biologically-derived nanomaterials, and receptor-mediated transcytosis to facilitate targeted delivery. Furthermore, we discuss how critical physicochemical properties—such as nanoparticle size, surface charge, and functionalization—dictate barrier penetration efficacy. The integration of multifunctional platforms that combine therapeutic and diagnostic capabilities is also highlighted. The discussion is supported by an analysis of recent preclinical studies and clinical translations that demonstrate promising outcomes. Finally, we address the persistent challenges of scalability, biocompatibility, and long-term toxicity that accompany these emerging technologies. Future progress in this field hinges on the development of advanced biomimetic nanocarriers and precision-targeting strategies to improve specificity and reduce off-target effects. Overcoming translational bottlenecks through standardized evaluation protocols and comprehensive safety profiling will be essential for clinical adoption. Ultimately, continued interdisciplinary collaboration is vital to fully realize the potential of nanomedicine in revolutionizing the treatment of brain cancers and other neurological disorders.

Keywords: Blood-brain barrier, Drug delivery, Glioblastoma, Nanomedicine, Neuro-oncology, Receptor-mediated transcytosis

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Introduction

BBB serves as a critical protective mechanism for the central nervous system (CNS), selectively allowing the passage of essential nutrients while blocking harmful substances [1-5]. The challenge of crossing the BBB remains a significant obstacle in the effective treatment of neuro-oncological conditions, prompting extensive research into nanomedicine strategies designed to overcome this biological barrier [6-10]. The BBB's restrictive nature, which protects the brain from circulating harmful agents, also impedes therapeutic agents, including chemotherapeutics and immunomodulators, from reaching intracranial targets [11]. Consequently, innovative nanotechnology-based approaches are being developed to facilitate drug delivery across this barrier. One prominent strategy involves exploiting BBB receptors and transporters to enhance nanoparticle translocation. Moura et al. [11] highlight the importance of understanding the structure and function of these receptors to develop targeted nanocarriers that can engage specific transport mechanisms. Similarly, Pinheiro et al. [12] emphasize the necessity of designing nanoparticles capable of BBB passage to reach targeted brain regions effectively. These receptor-mediated approaches are central to improving nanomedicine delivery efficiency in neuro-oncology.

Physicochemical properties of nanocarriers significantly influence their ability to traverse biological barriers, including the BBB [13-17]. Wang et al. [18] discuss how parameters such as particle size, surface charge, morphology, and surface modifications can be tailored to optimize barrier penetration. For instance, surface modifications can enhance nanoparticle stability and facilitate receptor engagement, thereby improving brain uptake. Such insights are critical for designing nanomedicines capable of crossing the BBB in neuro-oncological applications. In addition to receptor targeting and physicochemical optimization, various nanoparticle platforms have been explored. Cunha et al. [19] review the use of poly(lactic-co-glycolic acid) (PLGA)-based nanoparticles for neuroprotective drug delivery, demonstrating their potential to bypass biological barriers and deliver therapeutic agents effectively. Similarly, Khilar et al. [20] provide a comprehensive

overview of nanomedicine strategies, including chemotherapy, immunotherapy, and advanced techniques like focused ultrasound, to facilitate BBB crossing in brain tumor treatment. These approaches underscore the multifaceted nature of nanomedicine strategies aimed at overcoming the BBB.

Gold nanoparticles have garnered particular interest due to their unique properties. Tarantino et al. [21] discuss the role of gold nanoparticles as therapeutic enhancers in brain cancer treatment, emphasizing their capacity to improve drug delivery and therapeutic efficacy across the BBB. Their ability to be functionalized with targeting ligands makes them promising candidates for neuro-oncological applications. Furthermore, the review by Khilar et al. [20] underscores the ongoing development of nanomedicine protocols that integrate various modalities such as chemotherapy, immunotherapy, and radiotherapy, often employing nanocarriers to facilitate BBB penetration. These integrated strategies aim to enhance therapeutic outcomes by ensuring adequate drug concentrations within brain tumors.

In summary, current nanomedicine strategies for crossing the BBB in neuro-oncology focus on receptor-mediated targeting, physicochemical optimization of nanocarriers, and multifunctional nanoparticle platforms. These approaches are supported by a growing understanding of BBB biology and nanocarrier design principles, offering promising avenues for improving treatment efficacy in brain tumors.

Understanding the BBB

The BBB is composed of tightly packed endothelial cells that form a physical barrier, preventing the entry of most therapeutic agents into the brain. This barrier is not only a structural impediment but also a dynamic interface that regulates the transport of molecules through various mechanisms, including receptor-mediated transcytosis and passive diffusion [22-26]. The complexity of the BBB necessitates innovative approaches to facilitate drug delivery, particularly for large molecules and nanoparticles.

Key components of the BBB

- Endothelial cells: These cells form the primary structural component of the BBB, lining the cerebral microvasculature. They possess tight junctions that restrict paracellular transport, thus maintaining the barrier's selective permeability [27-29].

- Pericytes: Embedded in the basement membrane, pericytes regulate blood flow, clearance of cellular debris, and the formation of tight junctions. They play a crucial role in maintaining BBB integrity and function [27, 30].

- Astrocytes: The end-feet of astrocytes envelop the blood vessels, providing biochemical support to endothelial cells and contributing to the regulation of blood flow and the maintenance of the BBB's selective permeability [27, 28, 31].

- Basement membrane: This extracellular matrix provides structural support and separates endothelial cells from pericytes and astrocytes, playing a role in the overall stability and function of the BBB [30, 32].

- Neurovascular unit: The neurovascular unit includes neurons, microglia, and other supporting cells, which work in concert with the BBB to regulate CNS homeostasis and respond to changes in the environment [28, 29].

Functions of the BBB

- Selective permeability: The BBB selectively allows the passage of essential nutrients and ions while restricting the entry of potentially harmful substances, such as toxins and pathogens [33, 34].

- Transport regulation: Specialized transport systems within the BBB facilitate the movement of glucose, amino acids, and other vital molecules into the brain, while efflux transporters remove waste products and xenobiotics [29, 35].

- Immune surveillance: The BBB regulates the trafficking of immune cells, allowing for immune surveillance while preventing excessive inflammation that could damage neural tissue [30, 36].

- Homeostasis maintenance: By controlling the ionic composition and pH of the brain's extracellular environment, the BBB ensures optimal conditions for neuronal activity and synaptic function [34, 36].

Physiological and pathological factors

- The BBB is composed of brain microvascular endothelial cells that form tight junctions, regulating the transport of substances and maintaining brain homeostasis [37, 38].

- Disruption of the BBB is associated with various neurological disorders, including Alzheimer's disease and Parkinson's disease, where increased permeability allows harmful substances to enter the brain [39, 40].

- Research is focused on understanding the molecular mechanisms underlying BBB dysfunction, such as the role of junctional proteins and their redistribution, which can lead to increased permeability and disease progression [37, 39].

- The integrity of the BBB is a crucial determinant of drug delivery efficacy. Pathological conditions can alter BBB permeability, affecting drug transport. For instance, diseases like neurodegenerative disorders and brain tumors can modify the BBB, impacting drug delivery strategies [41, 42].

- The BBB utilizes various transport mechanisms, including receptor-mediated transcytosis and carrier-mediated transport, which can be harnessed for drug delivery. Understanding these mechanisms is essential for designing effective delivery systems [43, 44].

Drug delivery strategies

The nasal-to-brain route offers a non-invasive strategy for drug delivery, utilizing the olfactory and trigeminal nerve pathways to bypass the BBB. This method has shown potential in increasing drug residence time and therapeutic effectiveness [45, 46]. Techniques such as focused ultrasound-mediated BBB disruption and convection-enhanced delivery provide alternative routes for drug administration, allowing for direct access to the CNS [46, 47].

- Novel drug delivery strategies are being developed to enhance the transport of therapeutics across the BBB. These include the use of nanoparticles, which can improve the stability and bioavailability of drugs [48, 49].

- Carrier-based systems, such as nanoparticles and cell-based delivery, are being explored to facilitate the crossing of the BBB and target CNS disorders effectively [40, 48].

- Nanoparticles, such as liposomes, polymeric micelles, and

dendrimers, have shown promise in enhancing drug penetration and targeting capabilities. These systems can be engineered to improve solubility, stability, and bioavailability of drugs [45, 46].

- Nanoparticles can exploit receptor-mediated transcytosis, a natural transport mechanism across the BBB, by attaching ligands that mimic endogenous molecules [50, 51].

- Techniques such as focused ultrasound can temporarily open the BBB, allowing nanoparticles to deliver drugs directly to the brain [51].

- Modifying drugs chemically, such as through prodrugs or drug-polymer conjugates, can enhance their ability to cross the BBB. These modifications can improve drug lipophilicity and facilitate transport across the barrier [43, 52].

- Surface functionalization: Functionalizing nanoparticles with targeting ligands can enhance their specificity and binding affinity to BBB receptors, improving delivery efficiency. This approach is particularly useful in receptor-mediated drug delivery systems [42, 53].

- Strategies to temporarily disrupt the BBB or modify drugs to enhance their permeability are also under investigation, aiming to improve the therapeutic effect of CNS-active drugs [40, 49].

While significant progress has been made in developing strategies to overcome the BBB, the complexity of this barrier and the diversity of CNS disorders necessitate a multifaceted approach. Future research should aim to integrate these strategies, leveraging advances in materials science and biotechnology to create more effective and targeted drug delivery systems. This will be crucial in addressing the growing burden of neurological diseases and improving patient outcomes.

Nanomedicine Approaches to Cross the BBB

Nanomedicine offers innovative strategies to overcome the BBB, a significant obstacle in treating CNS diseases. The BBB's selective permeability limits drug delivery to the brain, necessitating advanced approaches to ensure effective treatment. Nanoparticles have emerged as a promising solution due to their ability to be engineered for targeted delivery, enhancing drug bioavailability and minimizing systemic toxicity [54-60].

Cell permeable peptides

Cell permeable peptides have emerged as a promising strategy for delivering neuroprotective agents across the BBB. Cell permeable peptides can effectively transport a variety of bioactive compounds into cells, offering potential therapeutic benefits in neurodegenerative diseases [61]. Their ability to block protein-protein interactions further enhances their clinical applicability, making them a valuable tool in neuro-oncology. Studies demonstrated that peptide conjugation significantly enhances BBB crossing and targeting specificity, with dual or multivalent modifications often yielding superior results [62-64]. Some studies highlighted variability in peptide performance between *in vitro* and *in vivo* models, emphasizing the importance of receptor specificity and peptide stability [65]. Branched or multivalent peptide designs improve permeability and transport efficiency compared to linear peptides [66, 67]. Peptides derived from viral proteins or natural ligands (e.g., RVG29, Angiopep-2 (AP2)) show high functionalization efficiency and receptor-mediated uptake [62, 68, 69].

Cell permeable peptides have demonstrated enhanced nanoparticle transport across the BBB, with studies showing improved neuronal transfection and brain accumulation using peptides such as trans-activator of transcription (TAT), RVG29, and AP2 [62, 63, 70]. The versatility of cell permeable peptides allows for conjugation to various nanocarriers, facilitating intracellular delivery and overcoming endosomal entrapment [71, 72]. Despite promising results, cell permeable peptides often suffer from rapid degradation *in vivo* and limited specificity, leading to off-target effects and potential toxicity [73]. Variability in peptide performance between *in vitro* and *in vivo* models complicates efficacy assessment, as seen with differing peptide behaviors in cellular uptake versus animal studies [65]. The short half-life and susceptibility to proteolysis remain significant hurdles [73].

Biologically-derived nanomaterials

Biologically-derived nanomaterials, such as liposomes and dendrimers, have shown great promise in overcoming the BBB. These materials are inherently biocompatible and can be surface-functionalized to enhance targeting capabilities. Their ability to self-assemble and degrade in biological environments makes them suitable candidates for drug delivery systems aimed at CNS diseases [74]. Most studies report favorable biocompatibility profiles for biologically-derived nanomaterials, including lipid nanoparticles, polymeric carriers, and exosomes, with low toxicity and immune response [70, 75, 76]. Stability and low hemolytic potential are critical for *in vivo* applications, as demonstrated in liposomal and polymeric systems [63, 77]. Some concerns remain regarding peptide conjugate immunogenicity and potential toxicity, necessitating further safety evaluations [73, 78]. Nanocarriers functionalized with endogenous ligands or biomimetic coatings tend to exhibit improved biocompatibility and reduced off-target effects [79, 80].

Biomimetic nanocarriers, such as ApoE-reconstituted lipoproteins and red blood cell membrane-coated nanoparticles, exhibit enhanced BBB penetration and targeted delivery to pathological sites, including amyloid-beta plaques and dopaminergic neurons [79, 80]. These systems benefit from inherent biocompatibility and reduced immunogenicity [76, 81]. The complexity of biological nanomaterials poses challenges in reproducibility and large-scale manufacturing. Additionally, their interactions with the immune system and potential for unexpected biodistribution require thorough investigation [73, 82]. The precise mechanisms of BBB crossing and long-term safety profiles are not fully elucidated, limiting clinical translation [73, 76].

Receptor-mediated transcytosis

Exploiting the natural transport mechanisms of the BBB, such as receptor-mediated transcytosis, presents a viable strategy for delivering therapeutic agents. By functionalizing nanoparticles with ligands that target specific BBB receptors, researchers can enhance the uptake of drugs into the brain [11]. This approach not only improves drug delivery efficiency but also minimizes systemic side effects. Receptor-mediated transcytosis via transferrin receptor (TfR), LDLR-related protein-1 (LRP-1), insulin receptor, and lactoferrin receptor is the predominant mechanism exploited by nanomedicines [62, 83, 84, 85]. Adsorptive-mediated transcytosis and shuttle-mediated pathways also contribute, especially for cell-penetrating peptides and viral-derived ligands [86-88]. Multivalent ligand presentation enhances receptor binding and transcytosis efficiency [67, 89]. Some nanocarriers utilize dual receptor targeting or combined mechanisms to overcome receptor saturation and improve BBB crossing [63, 77].

Receptor-mediated transcytosis-based strategies exploit endogenous BBB receptors (e.g., Tf, low-density lipoprotein receptor (LDLR), insulin receptors) to facilitate targeted nanoparticle

transport, with multivalent ligand presentation enhancing uptake [67, 83, 84]. Acid-cleavable linkages improve release and reduce endothelial retention [89]. Several studies demonstrate effective brain accumulation and therapeutic benefits in disease models [90-92]. Receptor saturation and competition with endogenous ligands can limit transport efficiency. High-affinity antibodies may be trafficked to lysosomes, reducing delivery efficacy [89]. Heterogeneity in receptor expression across brain regions and disease states complicates targeting [83]. Furthermore, the potential for receptor-mediated toxicity and off-target effects necessitates careful ligand design [73].

Nanoparticle design and modification

The physicochemical properties of nanoparticles, including size, surface charge, and hydrophilicity, play a crucial role in their ability to cross the BBB (Table 1). Recent studies have highlighted the importance of optimizing these properties to enhance the transport of nanoparticles across biological barriers [18]. For instance, mesoporous silica nanoparticles have been engineered to improve their drug loading and release profiles, thereby increasing their therapeutic efficacy [18]. Optimal nanoparticle size for BBB penetration is generally below 150 nm, with smaller sizes (20 to 60 nm) showing enhanced transcytosis and brain accumulation [75, 89, 93]. Surface charge and PEGylation length critically influence nanoparticle circulation time, cellular uptake, and BBB exocytosis [93, 94]. Ligand density and multivalency on nanoparticle surfaces modulate receptor binding avidity and intracellular trafficking [67, 92]. Nanoparticles are engineered with stimuli-responsive features (e.g., matrix metalloproteinase-sensitive liposomes) for controlled release in pathological brain environments [77].

Advances in nanoparticle engineering (Table 2), including size optimization (<150 nm), PEGylation with controlled chain length, and mixed functionalization strategies, have been correlated with improved BBB permeability and circulation time [75, 94, 95]. Surface decoration with peptides, antibodies, and surfactants enhances targeting and reduces hepatic accumulation [62]. The lack of standardized protocols for evaluating nanoparticle BBB penetration leads to interstudy variability and challenges in benchmarking efficacy [75]. Surface modifications may induce immunogenicity or alter pharmacokinetics unpredictably [73]. Additionally, balancing stealth properties with targeting efficiency remains complex, as excessive PEGylation can hinder cellular uptake [94].

Clinical translation potential

Several nanomedicine platforms have demonstrated promising preclinical efficacy and safety, with some advancing to clinical trials for CNS diseases [84, 93, 96]. Challenges remain in scalability, reproducibility, and comprehensive toxicity profiling, particularly for peptide-functionalized systems [73, 82]. Standardization of evaluation protocols and quantitative *in vivo* delivery monitoring are needed to facilitate translation [75, 76]. Multifunctional and biomimetic nanocarriers show enhanced translational potential due to improved targeting and biocompatibility [79, 80].

Many nanocarriers demonstrate low cytotoxicity and hemolytic potential *in vitro*, with some formulations showing favorable biodistribution and minimal off-target accumulation [63, 70, 77]. The use of biodegradable polymers and endogenous ligands contributes to safety profiles [97, 98]. Comprehensive *in vivo* toxicity data are often lacking, and long-term effects remain underexplored [73, 82]. Immunogenic responses to peptide conjugates and nanoparticle components pose risks [99]. Scalability, cost-effectiveness, and regulatory hurdles impede clinical translation despite promising preclinical outcomes [82, 100]. The complexity of CNS diseases and BBB variability further complicate therapeutic efficacy in humans [81].

In summary, while nanomedicine presents promising strategies for crossing the BBB, challenges remain in optimizing nanoparticle design

Table 1: Impact of nanoparticle physicochemical properties on BBB penetration.

Property	Optimal characteristic	Effect on BBB penetration and biodistribution
Size	<150 nm (ideal: 20 to 60 nm)	Smaller sizes favor enhanced transcytosis and brain accumulation; larger particles are more easily filtered by the spleen and liver
Surface charge	Neutral or slightly negative	Neutral charges reduce non-specific protein adsorption and opsonization, prolonging circulation; highly positive charges can cause toxicity
Surface coating	PEGylation (with optimized chain length)	Provides 'stealth' properties, reduces immune clearance, and enhances circulation time. Excessive PEG can hinder cellular uptake
Ligand density	Optimal, balanced density (multivalency preferred)	Low density may not trigger efficient receptor-mediated transcytosis; very high density can lead to aggregation and 'binding-site barrier'
Shape	Spherical or elongated	Spherical shapes are most common and easier to fabricate; specific elongated shapes may exhibit improved margination and flow dynamics
Hydrophobicity	Balanced/amphiphilic	Governs interaction with biological membranes; excessive hydrophobicity promotes opsonization; hydrophilicity aids solubility and circulation

Table 2: Comparison of nanocarrier platforms for brain delivery.

Nanocarrier type	Composition	Advantages	Limitations/challenges
Liposomes	Phospholipids, cholesterol	High biocompatibility; tunable size; can encapsulate both hydrophilic and hydrophobic drugs	Low stability; potential for drug leakage; scalability issues
Polymeric nanoparticles	PLGA, polylactic acid, Chitosan, etc.	Controlled release kinetics; high drug loading; biodegradable	Potential polymer toxicity (e.g., PLGA acidification); complex fabrication
Dendrimers	Synthetic branched polymers	Monodisperse size; multivalent surface for functionalization	Toxicity concerns of certain generations; complex and expensive synthesis
Gold nanoparticles	Metallic gold core	Tunable optics (e.g., for imaging); easy functionalization; photothermal properties	Non-biodegradable; long-term toxicity concerns; high cost
Micelles	Amphiphilic block copolymers	High solubility for hydrophobic drugs; small size (<50 nm)	Low stability upon dilution; critical micelle concentration can lead to disassembly *in vivo*
Exosomes	Biological lipid bilayer	Innate biocompatibility and low immunogenicity; natural targeting abilities	Difficulties in isolation, purification, and large-scale production; heterogeneous population

and ensuring safety and efficacy in clinical settings. The complexity of the BBB and the need for precise targeting necessitate continued research and development. Additionally, the potential for immune responses and long-term toxicity must be carefully evaluated to ensure the safe translation of these technologies into clinical practice.

Clinical Studies

Nanomedicine approaches to crossing the BBB have shown significant promise in clinical studies, particularly for treating CNS disorders such as glioblastoma, Alzheimer's disease, and other neurological conditions. The BBB is a major obstacle in delivering therapeutic agents to the brain due to its selective permeability, which protects the brain from toxins but also limits drug delivery. Nanomedicine offers innovative solutions by utilizing nanoparticles and nanocarriers to enhance drug delivery across the BBB.

A study by Kaya et al. [100] focused on developing a non-invasive, targeted nanoparticle-mediated drug delivery system across a human BBB model. The researchers successfully encapsulated a model compound, Fitc-dextran, within PLGA nanoparticles. Fitc-dextran is a large molecular weight (70 kDa) and hydrophilic compound. The encapsulation efficiency achieved was over 60%. The surface of the PLGA nanoparticles was chemically modified with a DAS peptide. This DAS peptide was specifically designed to have an affinity for nicotinic receptors, particularly alpha 7 nicotinic receptors, which are located on the surface of brain endothelial cells. The attachment of the DAS peptide facilitates the transport of the nanoparticles across the BBB via receptor-mediated transcytosis. The study utilized an optimal triculture *in vitro* BBB model, which successfully replicates the *in vivo* BBB environmen. This model demonstrated high transendothelial electrical resistance values, specifically ≥230 Ω/cm², indicating a tight barrier. It also showed high expression of zone of inhibition protein, a key tight junction protein, further confirming the integrity of the BBB model. Using their optimal BBB model, the DAS-conjugated Fitc-dextran-loaded PLGA nanoparticles achieved a fourteen-fold higher concentration of transport compared to non-conjugated Fitc-dextran-PLGA nanoparticles. This significant increase demonstrates the effectiveness of the DAS ligand in targeting and transporting the nanoparticles across the BBB. The novel *in vitro* BBB model developed in this study is considered a viable method for high-throughput screening of potential therapeutic delivery systems to the CNS (Figure 1). This allows for the identification of lead therapeutic compounds, such as their receptor-targeted DAS ligand-conjugated nanoparticles, before progressing to more costly and time-consuming *in vivo* studies. In summary, the paper successfully demonstrated the development of a targeted PLGA nanoparticle system capable of efficiently encapsulating a hydrophilic compound and delivering it across a robust *in vitro* human BBB model, offering a promising platform for future CNS drug development.

A study by Han et al. [62] outlines the successful development and evaluation of peptide-functionalized lipid nanoparticles designed

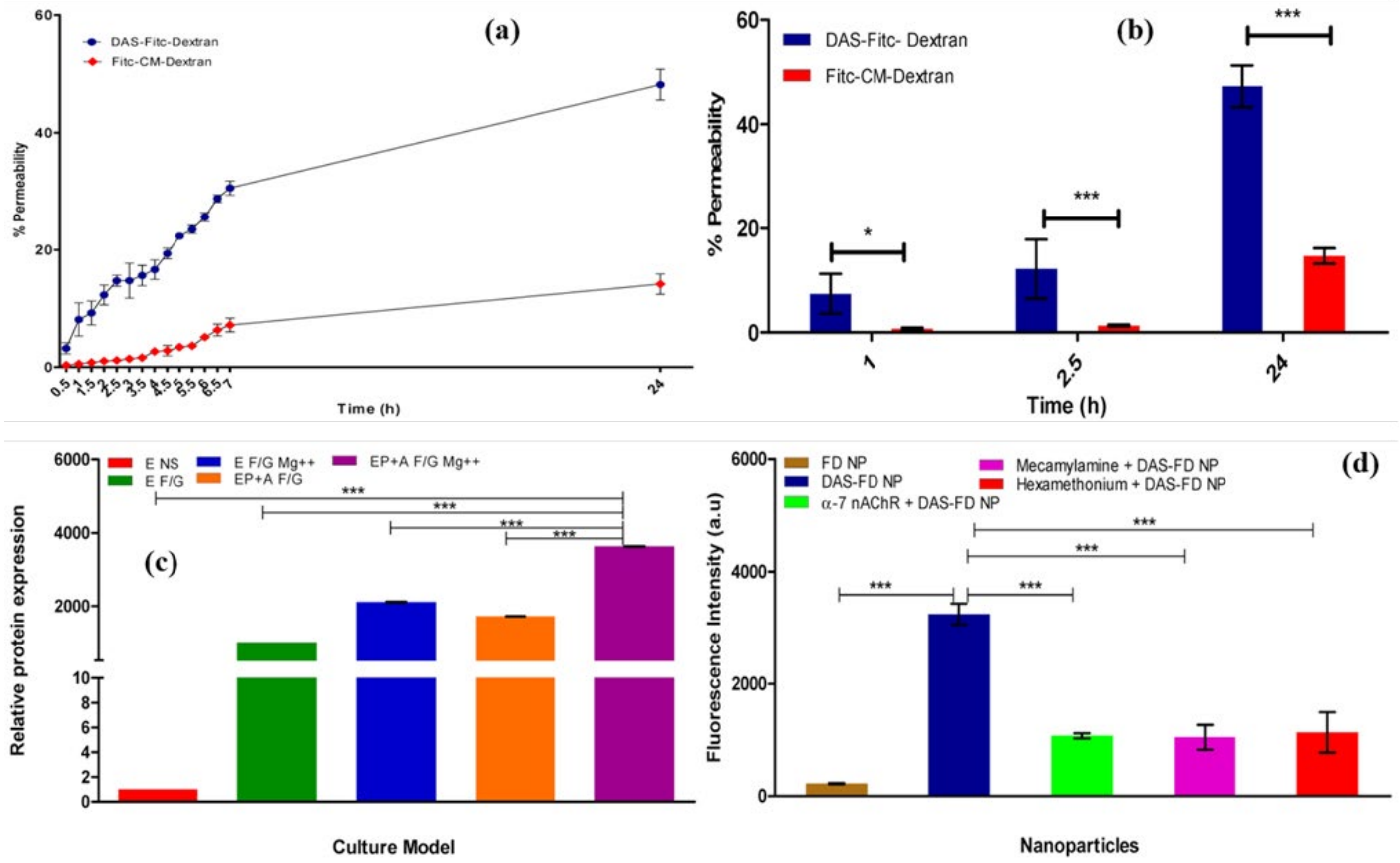

Figure 1: (a) Permeability (%) of DAS-Fitc-dextran and Fitc-dextran across the *in vitro* BBB model, measured over a 24 h period (λex 485 nm, λem 520 nm). **(b)** Permeability values for DAS-Fitc-dextran and Fitc-dextran at selected time points, as measured in the optimized *in vitro* BBB model. **(c)** Quantitative assessment of relative ZO1 protein expression levels in each BBB model. **(d)** Fluorescence intensity (a.u.) in the basolateral medium of the optimal BBB model 24 h after administration of Fitc-dextran NP and DAS-Fitc-dextran NP (λex 485 nm, λem 520 nm), including treatments with an α-7 nicotinic acetylcholine receptor antibody, mecamylamine, and hexamethonium [100].

for targeted mRNA delivery to the brain, overcoming challenges associated with the BBB and hepatic accumulation. The study utilized click chemistry to functionalize lipid nanoparticles with specific peptides. These peptides, including RVG29, T7, AP2, and mApoE, were chosen for their ability to target receptors overexpressed on brain endothelial cells and neurons. The researchers evaluated the impact of lipid nanoparticles targeting on brain endothelial and neuronal cell transfection *in vitro*. This evaluation included investigating factors such as serum protein adsorption, intracellular trafficking, endothelial transcytosis, and exosome secretion. Peptide functionalization of lipid nanoparticles was shown to enhance mRNA transfection in the mouse brain after systemic administration. The functionalized lipid nanoparticles also demonstrated a reduction in hepatic delivery, addressing a significant challenge in systemic delivery of nucleic acids. Specifically, RVG29 lipid nanoparticles were highlighted for improving neuronal transfection *in vivo*. This finding establishes RVG29 lipid nanoparticles' potential as a nonviral platform for delivering mRNA to the brain. In summary, the paper successfully demonstrated that peptide-functionalized lipid nanoparticles, particularly those functionalized with RVG29, can effectively deliver mRNA to the brain systemically, enhance neuronal transfection, and reduce off-target accumulation in the liver, thus presenting a promising nonviral platform for brain-targeted mRNA therapies.

A study by Rodrigues et al. [63] focused on the development and screening of brain-targeted lipid-based nanoparticles, specifically liposomes, designed for enhanced cell penetration and gene delivery. The peptides (pVec, QL, TAT) and Tf protein were successfully conjugated to DSPE-PEG2000-NHS, achieving coupling efficiencies ranging from 75.1% to 84.2%. Liposomal formulations had an average size of approximately 155 nm and exhibited a positive zeta potential. Surface modifications did not negatively impact the encapsulation efficiencies of plasmid DNA (pDNA), which consistently remained above 80%. Liposomal formulations containing chitosan-pDNA complexes effectively protected the encapsulated pDNA from enzymatic degradation by DNase I. The formulations exhibited low hemolytic potential, with an average of 1.4% hemolysis at the lowest phospholipid concentration (31.25 nM), increasing to 12.2% at 1,000 nM. Liposomal formulations showed low cytotoxicity in bEnd.3, glial, and primary neuronal cells at low phospholipid concentrations (100 nM), maintaining approximately 90% cell viability. Treatment of mice with liposomal formulations did not induce mortality or clinical signs of toxicity, and histological analysis of tissue sections showed no changes in morphology or signs of inflammation or cellular damage. A significant and time-dependent increase in liposomal uptake was observed in bEnd.3, glial, and primary neuronal cells, with uptake increasing from 0.1 to 4 h of incubation. Cellular internalization occurred via multiple endocytosis pathways, with energy-dependent endocytosis being the main mechanism. Clathrin-mediated endocytosis and macropinocytosis played significant roles, particularly for pVec-liposomes, while caveolae-mediated endocytosis also contributed. The extent of liposomal uptake was influenced by both liposome surface modifications and cell type. Dual-modified liposomes (e.g., pVec-Tf-lip, QL-Tf-lip, TAT-Tf-lip) showed higher inhibition of uptake after sodium azide pretreatment compared to single-modified liposomes. TAT-Tf-liposomes significantly enhanced the number of bEnd.3 (62.3%) and primary glial cells (41.3%) expressing GFP. They also resulted in significantly higher GFP expression in primary neuronal cells (12.8%) compared to other formulations and Lipofectamine 3000. Similarly, TAT-Tf-liposomes containing chitosan-pβgal complexes showed significantly higher ability to induce protein expression in bEnd.3, primary glial, and primary neuronal cells. TAT-Tf-liposomes demonstrated significantly higher transport across the *in vitro* BBB model compared to other liposomal formulations, with a 5-fold higher permeability coefficient than Na-F (a barrier integrity marker). The liposomes did not disrupt the *in vitro* barrier layer, as indicated by stable transendothelial electrical resistance levels throughout the transport detection. TAT-Tf-liposomes containing chitosan-pGFP complexes induced significantly higher GFP levels in primary neuronal cells after transport across the *in vitro* BBB model compared to pVec-Tf-lip and QL-Tf-lip. TAT-Tf-liposomes demonstrated superior efficiency in penetrating the brains of mice, with 7.7% ID/g of tissue found in the brain, compared to 3.1% ID/g for TAT-liposomes. This indicates stronger efficacy in brain targeting for dual-modified liposomes (Figure 2). The brain-targeted delivery of TAT-Tf-liposomes also implied a reduction of non-specific accumulations in the lungs and spleen. In conclusion, the study successfully developed and screened brain-targeted liposomal nanoparticles, identifying TAT-Tf-liposomes as a highly effective system for gene delivery to the brain. These nanoparticles demonstrated excellent protective properties, efficient cellular uptake, high transfection efficiency, and the ability to cross the BBB without compromising its integrity, suggesting their significant potential for brain-targeted gene therapy.

A study by Hou et al. [65] evaluated and compared the performance of 6 different peptides, categorized by whether they interact with specific receptors on the BBB or not. Peptides with BBB-specific receptors included T7, D-T7, and GSH. Peptides without BBB-specific receptors included trans-Golgi network, cis-Golgi network, and TAT. These peptides were conjugated to lipids, forming a shell around a core of PLGA and lamotrigine, creating nanoparticles for targeted epilepsy therapy. *In vitro* assays revealed that nanoparticles modified with TAT showed the highest internalization efficacy. This superior internalization was observed in bEnd·3 cells, which are a BBB model cell line, and in hippocampal neurons. In contrast to the *in vitro* findings, experiments conducted in mice demonstrated different results. D-T7-modified nanoparticles exhibited the highest brain targeting capability and achieved the most efficient epilepsy therapeutic effect *in vivo*. The experiments highlighted the varying performances of the 6 peptides at different levels of testing (*in vitro* vs *in vivo*). These findings provide valuable insights for the development of new delivery systems aimed at treating CNS diseases. In summary, the paper found a discrepancy between *in vitro* and *in vivo* results regarding the most effective peptide for BBB penetration and therapeutic efficacy. While TAT-modified nanoparticles showed the best internalization in cell models, D-T7-modified nanoparticles proved most effective for brain targeting and epilepsy treatment in live mice.

A study by Israel et al. [83] demonstrated that covalently attaching 6 different peptide vectors (AP2, B6, Miniap-4, D1, D3, and ACI-89) to a 50 kDa poly(β-l-malic acid)-trileucine polymer, forming P/LLL(40%)/vector conjugates, substantially increased their ability to cross the BBB. These vectors target specific transcytosis receptors, including LRP-1, TfR, bee venom-derived ion channel, and Aβ/LRP-1 related transcytosis complex. A two-step mechanism is proposed for the nanoconjugates' transcytosis: first, the copolymer group binds to the endothelial membrane; second, this binding induces an allosteric membrane rearrangement that exposes the sites for vector–receptor complex formation. Competition experiments with nonconjugated vectors confirmed the specificity of the vectors, while P/LLL(40%) did not act as an inhibitor, suggesting that the copolymer binding site is eliminated after vector-nanoconjugate binding. The brain delivery

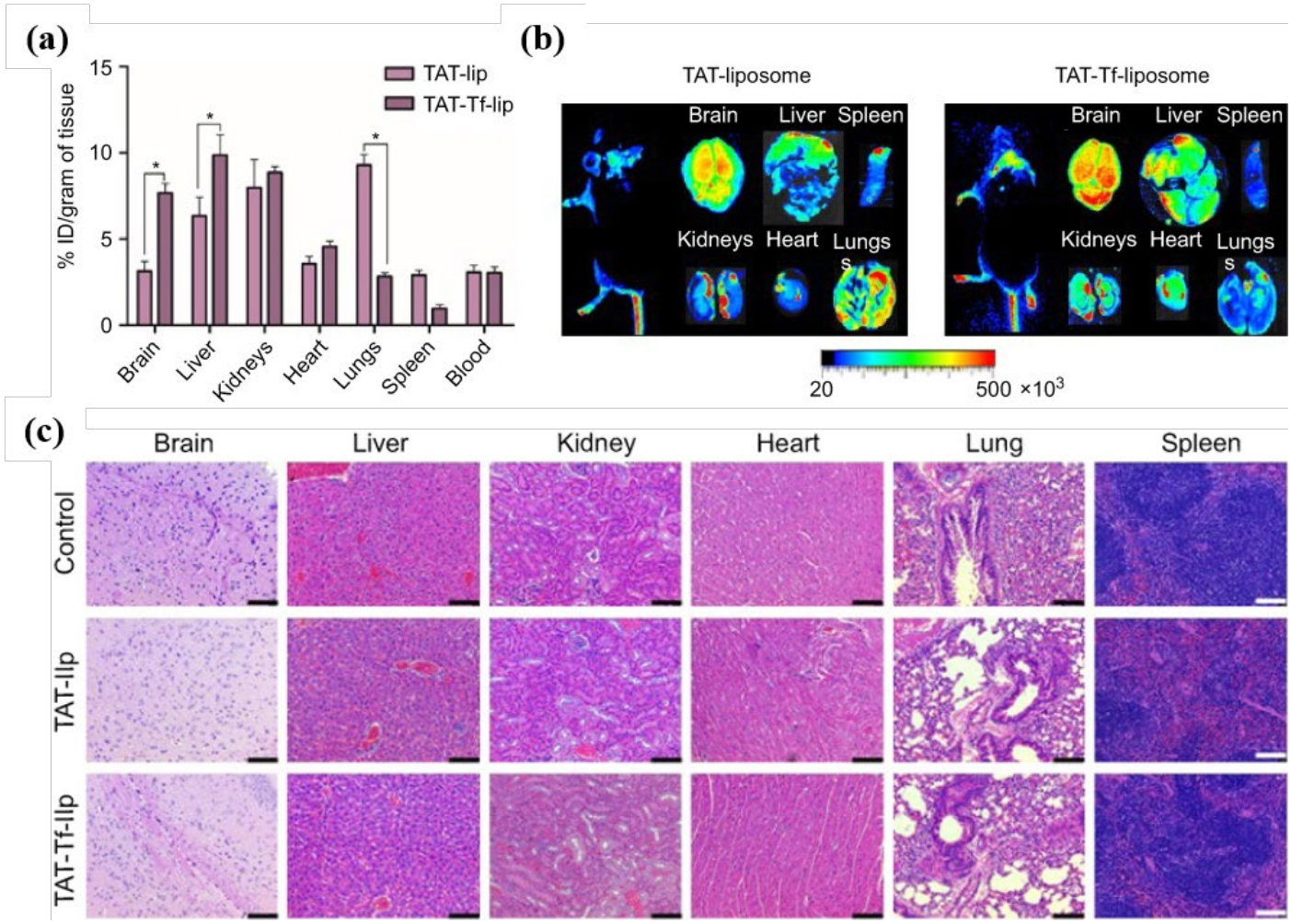

Figure 2: (a) Biodistribution in C57BL/6 mice 24 hours after injection with TAT-lip or TAT-Tf-lip, measured in the brain, liver, kidneys, heart, lungs, spleen, and blood. **(b)** Near-infrared fluorescence images showing the relative signal intensity in mice and in *ex vivo* organs (brain, liver, kidneys, heart, lungs, and spleen) 24 h post-injection with TAT-lip or TAT-Tf-lip. **(c)** Histological analysis (H&E staining) of organ sections (brain, liver, kidneys, heart, lungs, and spleen) from C57BL/6 mice treated with saline (control), TAT-lip, or TAT-Tf-lip via tail vein injection (n = 6) [63].

signatures of these nanoconjugates were evaluated in mouse models of normal, glioblastoma (tumor), and Alzheimer's disease. BBB permeation was most efficient in tumor models, followed by normal brains, and then Alzheimer's disease-like brains. In tumor-bearing and normal brains, AP2 was identified as the top-performing vector. However, in Alzheimer's disease models, D3 and D1 peptides demonstrated superior efficacy. The TfR vector B6 showed consistent efficiency in both normal and Alzheimer's disease-model brains. The study also noted that cross-permeation efficacies are influenced by modulated vector colligation and dosage escalation, leading to supra-linear dose dependence and crossover transcytosis activities. In summary, the paper highlights the successful development of vector-guided nanoconjugates that significantly enhance BBB permeation through a novel two-step mechanism. The efficacy of these nanoconjugates and their specific peptide vectors varies considerably across normal, tumor, and Alzheimer's disease brain models, suggesting the potential for targeted therapeutic delivery based on disease state.

While nanomedicine offers promising strategies for crossing the BBB, it is important to consider the broader implications and potential limitations. The complexity of the BBB and the variability in disease pathology across patients pose significant challenges. Additionally, the long-term effects and potential toxicity of nanoparticles need thorough investigation. As research progresses, a multidisciplinary approach involving collaboration between scientists, clinicians, and regulatory bodies will be essential to fully realize the potential of nanomedicine in treating CNS disorders.

Challenges and Future Directions

Despite the promising advancements in nanomedicine, several challenges remain in the clinical translation of these technologies. Issues such as nanotoxicity, stability, and the potential for unintended biodistribution must be addressed to ensure the safety and efficacy of nanoparticle-based therapies [21]. Furthermore, the heterogeneity of brain tumors and the presence of the blood-brain tumor barrier complicate treatment strategies, necessitating the development of multifunctional nanoparticles capable of targeting specific tumor microenvironments [101].

Challenges in crossing the BBB

- Structural and functional barriers: The BBB is a highly

selective barrier composed of endothelial cells, tight junctions, and various transport mechanisms that restrict the passage of large molecules, including nanoparticles and monoclonal antibodies, into the brain [102].

- Targeting specificity: Designing nanocarriers that can specifically target diseased neurons without affecting healthy ones is a significant challenge. This is crucial for minimizing off-target effects and potential neurotoxicity [22].

- Biological interactions: Understanding the complex interactions between nanocarriers and biological systems, including the immune response and the potential for nanoparticle aggregation, is essential for optimizing delivery systems [103].

- Clinical translation: Despite advances in preclinical studies, few nanomedicine strategies have successfully transitioned to clinical trials. This is due to challenges in scaling up production, ensuring long-term safety, and achieving consistent therapeutic outcomes [104].

Future directions in nanomedicine

- Advanced targeting strategies: Techniques such as receptor-mediated transcytosis and focused ultrasound are being explored to enhance the delivery of nanomedicines across the BBB. Receptor-mediated transcytosis, in particular, has shown promise in facilitating the transport of large molecular cargos [22, 102].

- Multifunctional nanocarriers: The development of multifunctional nanocarriers that combine therapeutic and diagnostic capabilities (theranostics) could improve treatment outcomes by allowing for real-time monitoring of drug delivery and efficacy [105].

- Reactive oxygen species-based Therapies: Reactive oxygen species-based nanotherapies, such as photodynamic and chemodynamic therapies, offer novel approaches for treating gliomas by generating reactive oxygen species within tumor cells, thereby enhancing therapeutic efficacy [106].

- Precision medicine: Leveraging the principles of precision medicine to design cascade-targeted nanomaterials that can overcome multiple biological barriers holds potential for improving the specificity and effectiveness of brain-targeted therapies [104].

While the potential of nanomedicine to revolutionize CNS disorder treatment is significant, it is important to consider the broader context of these developments. The complexity of the BBB and the CNS itself present inherent challenges that require interdisciplinary approaches and collaboration across fields such as materials science, pharmacology, and neurology. Additionally, ethical considerations and regulatory hurdles must be addressed to ensure the safe and effective implementation of these technologies in clinical settings. As research progresses, a balanced approach that integrates innovative scientific advancements with practical clinical applications will be crucial for the successful translation of nanomedicine strategies into effective treatments for CNS disorders.

Conclusion

The literature underscores that nanomedicine strategies employing cell-penetrating peptides, biologically-derived nanomaterials, receptor-mediated transcytosis, and sophisticated nanoparticle design modifications have significantly advanced the capacity to traverse the BBB for effective CNS drug delivery. Peptide functionalization consistently emerges as a critical facilitator of BBB crossing, enhancing nanoparticle uptake, intracellular trafficking, and targeting specificity. Dual or multivalent peptide modifications further amplify transport efficiency and receptor engagement, although variability in *in vitro* versus *in vivo* performance and peptide stability remain challenges requiring optimization. Viral-derived and natural ligand-based peptides demonstrate high affinity and transcytosis efficacy, illustrating the merit of biomimicry in nanocarrier design.

Biologically-derived nanomaterials, including lipid-based nanoparticles, exosomes, and biomimetic carriers such as ApoE-reconstituted lipoproteins and red blood cell membrane-coated nanodecoys, offer superior biocompatibility and reduced immunogenicity, presenting promising platforms for clinical translation. These systems synergize inherent targeting capabilities with favorable pharmacokinetics, though manufacturing complexity and comprehensive safety profiling remain barriers to widespread adoption. Receptor-mediated transcytosis is the predominant pathway leveraged by nanomedicines, targeting receptors such as Tf, LDLR, insulin, lactoferrin, and LRP-1. Multivalent ligand presentation and acid-cleavable linkages optimize receptor binding and intracellular trafficking to minimize endothelial retention and lysosomal degradation. However, receptor saturation, competition with endogenous ligands, regional receptor heterogeneity, and possible off-target effects necessitate careful receptor and ligand selection to maximize therapeutic index.

Nanoparticle physicochemical properties, particularly size below 150 nm, surface charge, PEGylation length, ligand density, and stimuli-responsive modifications, critically influence BBB penetration, circulation time, cellular uptake, and drug release kinetics. Longer polyethylene glycol (PEG) chains enhance systemic circulation and BBB exocytosis, while optimal ligand density balances receptor avidity with efficient transcytosis. Surface engineering strategies must finely tune stealth properties with targeting efficacy to mitigate immune recognition and maintain pharmacokinetic stability.

Despite encouraging preclinical efficacy and safety data, clinical translation of nanomedicine approaches to CNS drug delivery faces challenges including scalable manufacturing, reproducible functionalization, standardized evaluation protocols, and thorough long-term toxicity assessments. Advanced *in vitro* BBB models and *in vivo* imaging techniques facilitate mechanistic insights and candidate screening but require harmonization to improve interstudy comparability and predictive validity for human physiology.

In conclusion, integrating optimized peptide functionalization, biologically-inspired nanocarriers, receptor-targeted transcytosis mechanisms, and rational nanoparticle engineering forms a robust multi-pronged framework for overcoming the BBB. Continued efforts to address translational bottlenecks, refine targeting specificity, and elucidate intracellular trafficking pathways will be vital to realizing the full therapeutic potential of nanomedicine for CNS disorders.

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None.

Conflict of Interest

None.

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