Nanoscale

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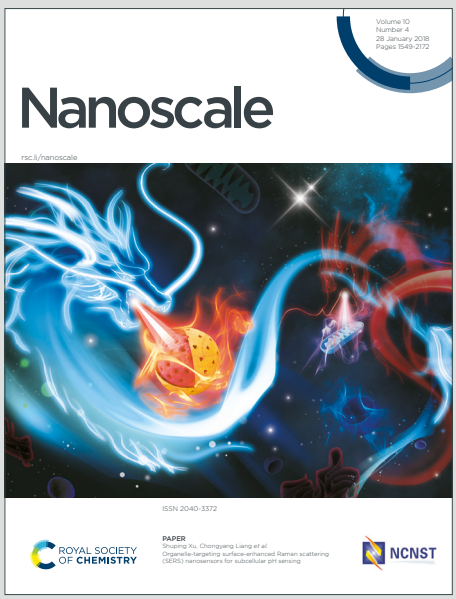
This article can be cited before page numbers have been issued, to do this please use: P. Bharadwaj, V. G. Roullin and J. Chain Leblond, *Nanoscale*, 2025, DOI: 10.1039/D5NR02548F.



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DOI: 10.1039/D5NR02548F

Crossing the Blood-Brain Barrier: Advances in Dendrimer-Based Nanocarriers for Central Nervous System Delivery

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Abstract

Dendrimer-based nanocarriers are emerging as transformative platforms to overcome the challenge of crossing the blood-brain barrier (BBB) in the treatment and diagnosis of central nervous system (CNS) disorders. Their highly branched, monodisperse architecture enables precise control over size, surface chemistry, and cargo loading, distinguishing them from conventional nanocarriers such as liposomes and polymeric nanoparticles. This review summarizes recent advances in designing dendrimers for targeted brain delivery across diverse neurological conditions. In particular, advances in dendrimer synthesis and functionalization including PEGylation, ligand conjugation, and biomimetic coatings have significantly improved BBB permeability, biocompatibility, and disease-specific targeting. Key dendrimer classes, including PAMAM, PPI, phosphorus, and peptide-based variants, exploit multiple BBB crossing mechanisms such as adsorptive-mediated, receptor- and carrier-mediated transcytosis. We then focus on therapeutic applications and clinical translation, highlighting candidates such as OP-101 and ^{18}F-OP-801, which demonstrate targeted delivery and imaging capabilities in neuroinflammatory and oncological models. Despite these advances, challenges remain in addressing dendrimer-associated toxicity, scalable manufacturing, and the heterogeneity of BBB dysfunction across disease states. Looking ahead, integrating artificial intelligence (AI) for BBB permeability prediction and the adoption of advanced biomimetic and aptamer-based targeting strategies could accelerate the development of next-generation dendrimer therapeutics.

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1. Introduction

The treatment and diagnosis of central nervous system (CNS) disorders continue to pose formidable challenges, primarily due to the presence of the blood-brain barrier (BBB). BBB is a dynamic and tightly regulated endothelial interface that maintains brain homeostasis by restricting the entry of potentially harmful substances, including over 98% of small-molecule drugs and nearly all large biologics [1]. Comprising specialized endothelial cells sealed by tight junctions, a basement membrane, astrocytic end-feet, and pericytes, the BBB effectively limits paracellular diffusion and regulates transcellular transport through selective mechanisms, thereby creating a major hurdle in the delivery of therapeutic agents for neurodegenerative diseases, brain tumors, ischemic injuries, and CNS infections [1]. To overcome these barriers, nanotechnology offers tailored strategies such as ligand conjugation for receptor-mediated transcytosis, optimized physicochemical properties for enhanced BBB permeability, and evasion of efflux pumps collectively improving drug delivery to the brain [2].

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Dendrimers are synthetic, nanosized polymers characterized by a highly branched, tree-like architecture with precise structural control. These molecules consist of three parts: a central core, iterative layers of branched units (referred to as "generations"), and functional surface groups that govern their physicochemical properties [3, 4]. Their well-defined, monodisperse structure enables drug loading through encapsulation within internal cavities or covalent conjugation to surface sites, which properties critically depend on dendrimer generation (e.g., higher generations offer greater encapsulation volume). The multivalent surface further allows for tunable modifications, such as PEGylation or targeting ligands, enhancing biocompatibility, cellular uptake, and the ability to traverse biological barriers, including the BBB [4]. PAMAM (PolyAMidoAMine), PPI (PolyPropylene Imine), phosphorus, carbosilane, and peptide-based dendrimers illustrate the diversity of chemical structures and physicochemical properties. As shown in Figure 1, the field has progressed through several landmark advances, from Vögtle's synthesis of the first cascade molecules in 1978 to Tomalia's introduction of PAMAM dendrimers in 1985, early demonstrations of ligand-mediated BBB crossing in the mid-2000s, and the first reports of PAMAM–NAC conjugates penetrating injured brain tissue in 2010. More recently, translational milestones include the initiation of OP-101 clinical trials for neuroinflammation in 2018 and the development of ^{18}F-OP-801 for CNS imaging in 2021. This historical trajectory highlights how innovations in dendrimer chemistry, functionalization, and application have progressively expanded their potential for CNS-targeted therapeutics.

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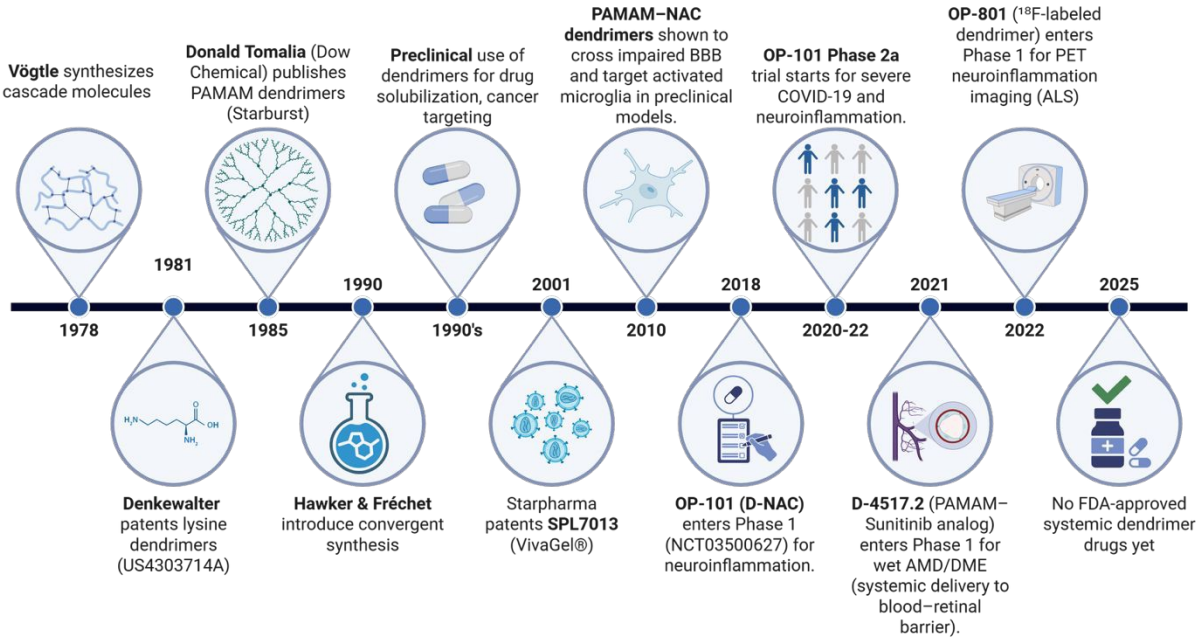

Figure 1: Timeline of dendrimer development and translation toward blood–brain barrier (BBB) and systemic therapeutic applications.Created with Biorender. Abbreviations: PAMAM, poly(amidoamine); NAC, N-acetylcysteine; BBB, blood–brain barrier; SPL70mu13, Starpharma dendrimer antiviral; AMD, age-related macular degeneration; DME, diabetic macular edema; PET, positron emission tomography; ALS, amyotrophic lateral sclerosis.[5-13] NCT04321980; [14-16]

Several nanoparticle-based nanocarriers have been recently reviewed for traversing the BBB [17]. Polymeric micelles self-assemble from amphiphilic block copolymers and solubilize hydrophobic drugs with high efficiency, though their passive BBB permeability is limited without active targeting [18]. Lipid nanoparticles (LNPs**)**, clinically validated for mRNA vaccines, can be engineered with targeting ligands or ionizable lipids to improve CNS delivery, but their stability and off-target accumulation remain concerns [19]. Exosomes, naturally secreted extracellular vesicles, exhibit intrinsic biocompatibility, immune evasion, and innate BBB-crossing ability via endogenous receptor–ligand interactions; however, their clinical translation is hindered by low yield, heterogeneity, and complex isolation protocols [20]. Graphene quantum dots (GQDs), with ultrasmall size (<10 nm) and intrinsic fluorescence, show promise for theranostics through efficient BBB penetration and imaging capabilities, yet raise questions about long-term carbon-based nanomaterial safety [21]. Compared to these conventional nanotechnology platforms, dendrimers offer several distinct advantages. First, their monodispersity ensures uniform pharmacokinetics and biodistribution as compared to polymers, which is critical for reproducible

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therapeutic outcomes. Second, each successive generation increases the number of surface functional groups, allowing for multivalent interactions, which could improve cooperative binding effects with cell receptors or cell membranes, promoting internalization or transcytosis [22]. Third, the dendrimers hydrodynamic diameter range from 1–10 nm for lower generations (G0–G4) up to 20 nm for higher generations (G5–G7), making them comparable in size to proteins and enabling efficient endocytosis and diffusion across biological membranes [23]. This size is lower than liposomes or polymeric nanoparticles, with an improved chemical stability due to their unimolecular nature [24, 25]. Similarly to other nanoparticles, dendrimer enable the co-delivery of multiple cargos: their internal cavities provide sites for hydrophobic drug encapsulation, and their terminal surface groups can be precisely modified with hydrophilic drugs [26], shielding polymers, targeting ligands or imaging agents but on a single nanoscale scaffold.

Clinical translation of dendrimer-based systems is underway, with several candidates entering clinical trials. VivaGel® (SPL7013), a dendrimer developed to fight bacterial vaginosis [27], and DEP® docetaxel, designed for cancer therapy [28] have shown favorable safety and efficacy profiles. Notably, OP-101, a hydroxyl PAMAM dendrimer-N-acetylcysteine conjugate targeting neuroinflammation, is currently in Phase 2 clinical trials and has demonstrated targeted accumulation in activated microglia in multiple CNS models [29]. Beyond therapy, dendrimers have found increasing utility in diagnostics, especially as contrast agents for magnetic resonance imaging (MRI), computed tomography (CT) [30], and dual-modal imaging systems [10]. Multifunctional dendrimers loaded with gadolinium complexes [31], manganese [32], or radiolabeled moieties have facilitated high-resolution imaging the innate immune activation of the brain [33] with improved specificity and reduced systemic toxicity compared to conventional agents.

Given the breadth of applications and the versatility of dendrimer platforms, this review aims to comprehensively examine the recent advances in dendrimer design and their roles in traversing the BBB for both therapeutic and diagnostic of CNS diseases. We systematically discuss the types and generations of dendrimers employed, their surface modifications, mechanisms of BBB penetration, disease-specific applications, and their current status in preclinical and clinical settings. By integrating findings from basic science, preclinical evaluations, and translational

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studies, this review underscores the transformative potential of dendrimers in overcoming the BBB and advancing next-generation treatments for CNS disorders.

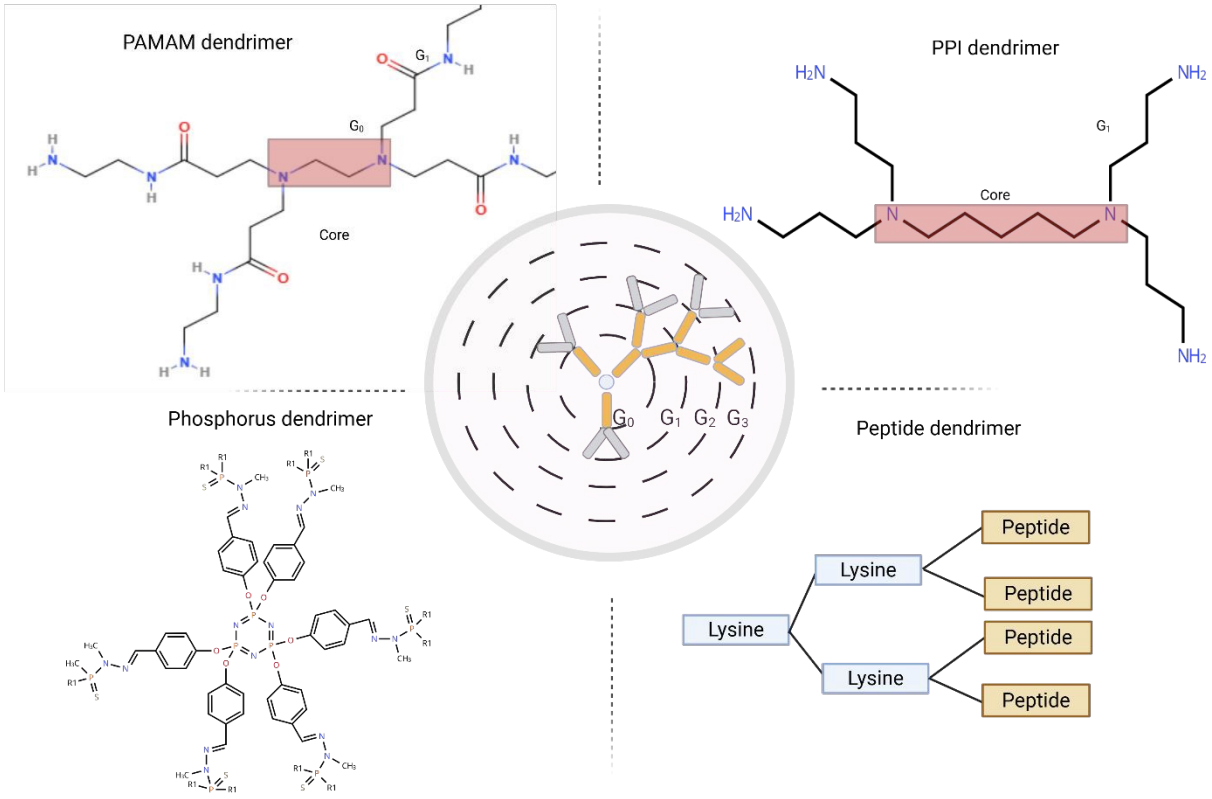

Figure 2: Schematic representation of dendrimer generation and chemical structure examples. Created with Biorender.

2. Dendrimer Types and Modifications

Main dendrimer classes explored for CNS diseases (PAMAM, PPI, phosphorus, and peptide-based) are presented in Figure 2 and Table 1**.** The clinical potential of dendrimers for CNS disorders hinges not only on their BBB-crossing capabilities but also on scalable manufacturing methods that ensure consistent quality. Fundamental differences in core structure, surface chemistry, and size distributions among dendrimer classes directly impact their manufacturability and biological performance. Recent advances in synthesis now enable precise control over dendrimer architecture, a critical factor determining their behavior at the BBB interface. While detailed chemical protocols fall outside this review's scope, we

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highlight key production strategies influencing translational success (Box 1) which must be tailored to each dendrimer class's unique properties.

Table 1: Comparative analysis of dendrimer classes for CNS drug delivery: Structural features, BBB penetration mechanisms, advantages, and clinical translation

Feature	*PAMAM Dendrimers*	*PPI Dendrimers*	*Phosphorus Dendrimers*	*Peptide-Based/Hybrid Dendrimers*
Core Structure	Ethylenediamine core, amidoamine branches	Diaminobutane core, propylene imine branches	Phosphorhydrazone core, organophosphorus branches	Amino acids, peptides, or hybrid (e.g., PEG, carbosilane)
Surface Groups	$–NH_2$, –OH, –COOH	Primary amines (often modified)	Amines, hydroxyls, peptides, radicals	Peptides, PEG, bioactive ligands
Size Range	~1 nm (G0) to 15 nm (G6–G7)	~2 nm (G1) to ~10 nm (G5)	~3 nm to ~12 nm (G1–G4)	Variable (2–20 nm)
BBB Penetration Mechanism	Adsorptive-mediated transcytosis (AMT, cationic), passive diffusion (neutral)	Charge-mediated (cationic), glycan-mediated transport	Ligand-receptor (e.g., RGD), passive diffusion	Receptor-mediated (peptide mimics), passive/active transport
Advantages	- Precise architecture - Multifunctional (drug delivery, imaging) -Tunable surface chemistry	- Compact, globular structure - High surface charge for electrostatic binding - Developed for brain tumors (e.g., paclitaxel delivery)	- Biodegradable backbone - Metal-free MRI contrast capability - Redox-active modifications	- Intrinsic bioactivity (e.g., neuroprotection) - Biomimetic targeting - Low immunogenicity
Limitations	- Cytotoxicity (amine-terminated) - Non-specific protein binding - Burst drug release - Low hydrophobic drug loading	- High cytotoxicity (unmodified) -Requires extensive surface shielding - Limited clinical translation	- Complex synthesis - Limited in vivo data - Few targeting studies	- Scalability challenges - Variable stability - Limited pharmacokinetic data
Clinical Status	Phase 2 trials (OP-101 for neuroinflammation)	Preclinical	Preclinical	Preclinical

2.1. Poly(amidoamine) PAMAM dendrimer

Poly(amidoamine) (PAMAM) dendrimers, first synthesized by Donald Tomalia and colleagues in 1985, represent the prototypical and most extensively studied dendritic architecture for biomedical applications [7]. These nanoplatforms have since become the gold standard for CNS delivery, with several candidates advancing to clinical trials (NCT05387837, NCT05395624, NCT04262076). Structurally, PAMAM dendrimers are constructed through iterative Michael addition and amidation steps, resulting in spherical,

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tree-like macromolecules with generations (G0–G7) that define their size, surface group density, and internal void space [34, 35]. The ethylenediamine core gives rise to a highly branched amide backbone, while terminal groups typically amines (–NH_2), hydroxyls (–OH), or carboxylates (–COOH) can be selectively modified to enhance biocompatibility, cargo loading, and targeting capabilities [34].

The choice of dendrimer generation is critical, as each tier (low-G [G0–G3], mid-G [G4–G5], high-G [G6–G7]) exhibits distinct physicochemical and biological profiles (Table 2). These generations range in hydrodynamic diameter from ~1 nm (G0) to 15 nm (G6–G7), sizes small enough to traverse tight endothelial junctions of the BBB [36]. However, steric constraints in G5+ dendrimers synthesis often lead to incomplete branching, structural defects, and aggregation, compromising monodispersity and batch reproducibility [37]. Higher-generation dendrimers exhibit uneven charge distribution due to their densely branched architecture, resulting in surface charge heterogenicity. This generates localized regions of opposite charges on the surface, which promotes electrostatic interactions between dendrimers, ultimately leading to aggregation. Consequently, while higher generations offer greater cargo capacity, their heterogeneity may limit in vivo utility, necessitating rigorous characterization or alternative synthetic strategies [38]. Lower generations (G2–G3) are favored for small-molecule delivery and reduced immunogenicity, whereas mid-to-higher generations (G4–G5) offer increased surface functionality for complex tasks like gene delivery or multimodal imaging.

Without modifications, PAMAM internal cavity can accommodate hydrophobic drugs and their cationic surface charge promotes cellular adhesion [39]. Cationic amine-terminated PAMAMs tend to exploit adsorptive-mediated transcytosis (AMT) due to electrostatic interactions with the negatively charged endothelial surface (see next section for mechanisms of BBB crossing) [40]. Nevertheless, the high cationic charge density of surface amines can disrupt cellular membranes, induce oxidative stress, activate complement and lead to hemolysis. This inherent cytotoxicity is a major limitation of high-generation or amine-terminated PAMAM variants. Additionally, native PAMAMs may suffer from non-specific interactions with serum proteins, resulting in off-target accumulation, and limited bioavailability [41, 42]. From a formulation perspective, low drug loading for hydrophobic molecules and burst release profiles also present challenges for therapeutic consistency [43].

To circumvent these issues, extensive surface engineering approaches have been developed. The choice of modification depends on dendrimer generation and the intended application (Table 2). PEGylation remains a widely used method to shield positive charges, improve solubility, and extend circulation time

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[44]. Another promising strategy for brain delivery, pioneered by the Kannan laboratory, involves the synthesis of G4- hydroxyl-terminated PAMAM dendrimers with ~90 surface OH groups (referred to as "90-OH PAMAMs"). These dendrimers significantly reduced cytotoxicity and enhanced biocompatibility, allowing for safe systemic administration. Most notably, 90-OH dendrimers tested in a rabbit model of cerebral palsy exhibit selective accumulation in activated microglia and astrocytes in neuroinflammatory conditions, bypassing healthy tissue and enhancing disease-specific targeting [45]. These insights have led to the clinical development of OP-101, a dendrimer–N-acetylcysteine conjugate, now in Phase 2 trials for neuroinflammatory conditions including cerebral palsy and severe COVID-19 [9]. Further functionalization includes ligand-based targeting, cleavable linkers, and stimuli-responsive designs that respond to pH, redox potential, or enzymatic environments to release their payload selectively. For example, G2 PAMAM dendrimers are complexed with albumin to deliver citicoline in stroke models, leveraging size and charge for efficient absorptive-mediated (AMT-)based transcytosis [46]. G4 and G5 generations are often selected for multifunctional designs: PEGylated G4 dendrimers labeled with Rhodamine B have been used to probe ischemia-induced BBB disruption [47], while G5 PAMAMs conjugated with siRNA via glutathione-sensitive linkers have achieved targeted gene knockdown in an orthotopic glioblastoma multiforme (GBM) tumor model in CX3CR-1GFP mice [48]. Moreover, dual-ligand G5 dendrimers functionalized with Angiopep-2 and GE11 have served as MRI/NIR imaging agents for brain metastases, underscoring their theranostic potential [49]. PAMAMs also interface flexibly with diagnostic applications. Their nanoscale size and multivalency allow the incorporation of imaging agents such as gadolinium complexes, gold nanoparticles, manganese ions, or radionuclides, facilitating MRI, CT, or SPECT-based visualization of brain pathology [16].

Together, the synthesis precision, structural adaptability, surface engineering potential, and mechanism-driven design of PAMAM dendrimers explain their prominence in CNS nanomedicine.

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Table 2: Comparative Table: PAMAM Dendrimer Generations, Functionalization Strategies, and Trade-offs

Parameter	*Low-G (G0–G3)*	*Mid-G (G4–G5)*	*High-G (G6–G7)*
Size (Diameter)	1–5 nm	5–10 nm	10–15 nm
Surface Groups	4–32 terminal amines	64–128 terminal amines	256–512 terminal amines
Charge Density	Low cationic charge (low cytotoxicity)	Moderate charge (balance needed)	High charge (high cytotoxicity)
Preferred Ligand Choice	Small ligands (e.g., glucose, phenylalanine)	Peptides (e.g., RGD, Angiopep-2), PEG	Large/complex ligands (e.g., antibodies)
Functionalization Rationale	Minimize steric hindrance; ideal for small-molecule delivery	Optimize multivalency for targeting/drug loading	Requires shielding (e.g., PEGylation) to reduce toxicity
Advantages	-Small size enhances BBB penetration. - Low cytotoxicity (amine-terminated variants). - Minimal steric hindrance for small ligands.	- Optimal balance of size and functionality. - High surface group density for multivalent targeting. - AMT-mediated BBB crossing (cationic variants).	- High drug-loading capacity. - Enhanced EPR effect in tumors (leaky BBB).
Disadvantages	- Limited drug loading capacity. - Fewer sites for multivalent targeting.	- Moderate cytotoxicity (requires PEGylation). - Potential non-specific protein adsorption.	- Severe cytotoxicity (amine-terminated). - Steric crowding limits ligand accessibility. - Risk of aggregation.
Key challenges	Low payload capacity; rapid renal clearance.	Charge-mediated toxicity; complex synthesis.	Poor BBB penetration; manufacturing complexity.

2.2. Poly (propylene imine) Dendrimers (PPI)

Poly(propylene imine) (PPI) dendrimers, built from a diaminobutane (DAB) core and iteratively extended with propylene imine branches, gained attention for their high amine density and potential in drug delivery, gene transfection, and catalysis. PPI (Figure 1) dendrimers have been extensively studied for CNS applications. Structurally, PPI dendrimers are synthesized from a diaminobutane core via a repetitive double Michael addition of acrylonitrile followed by exhaustive hydrogenation, leading to highly branched macromolecules terminated with primary amines [50]. Compared to PAMAMs, PPI dendrimers have a slightly more compact and globular structure due to their propylene-based backbone and are often characterized by high surface charge density, making them suitable for electrostatic interaction-based transport across the BBB [51]. However, due to their inherent cytotoxicity at higher concentrations, extensive surface modification is often essential to render PPI dendrimers biocompatible and translationally viable.

In brain-targeted drug delivery, G4 PPI dendrimers have been modified with histidine and maltose ligands: histidine for BBB transcytosis and chelating ability for Cu^{2+} ions, especially relevant in Alzheimer's disease (since metal ion dyshomeostasis plays a detrimental role in oxidative stress related to disease

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progression), and maltose for neuroprotection and anti-amyloidogenic effects. This platform demonstrated effective in vivo BBB penetration (in APP/PS1 transgenic mice) and targeted neuroinflammatory regions without added drugs, emphasizing the therapeutic potential of the carrier itself [52].

Another landmark example leveraged G5 PPI dendrimers conjugated with sugars such as sialic acid, glucosamine, and concanavalin A to facilitate BBB crossing and deliver paclitaxel, a P-glycoprotein substrate, into Sprague-Dawley rats' brain tumors. *In vivo* studies revealed that such modified dendrimers enhanced paclitaxel accumulation in the brain by over 30-fold compared to free drug, likely due to ligand-mediated transcytosis in the disrupted BBB environment of gliomas [53]. Despite these early successes, PPI dendrimers have been largely supplanted by alternative dendritic systems, particularly PAMAM dendrimers, due to several critical limitations. The primary amine surface groups of PPI dendrimers confer substantially higher cytotoxicity compared to the tertiary amines of PAMAM dendrimers, causing membrane disruption, hemolysis, and inflammatory responses at therapeutic concentrations [54]. Although PPI dendrimers now occupy a niche role in catalysis [55], their historical contributions remain significant in the evolution of dendritic nanotechnology.

2.3 Phosphorus Dendrimers

Phosphorus dendrimers (Figure 2) offer inherent versatility in chemical modification and biodegradability. Unlike PAMAM and PPI dendrimers based on carbon-based backbones, phosphorus dendrimers feature a core of phosphorhydrazone units and phosphorus-centered branching points, which not only facilitate precise synthetic control but also allow the introduction of multiple functional groups: amines, hydroxyls, amides, at defined locations across the dendritic structure [56, 57].

These dendrimers have gained attention in CNS applications for their ability to be fine-tuned for biological interactions while retaining favorable pharmacokinetics. For instance, AK123 phosphorus dendrimer was functionalized with fibronectin for targeted therapy in Parkinson’s disease (PD). The RGD motif of fibronectin enabled selective binding to activated microglia and endothelial integrins, while the dendritic backbone allowed efficient crossing of the BBB. The resulting nanocomplex showed nearly 2-fold higher BBB penetration compared to fibronectin alone (details in Table 3) and modulated neuroinflammation effectively in PD mice models [58].

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Additionally, a novel G3 poly(phosphorhydrazone) dendrimer containing 48 stable PROXYL radical units was developed as a metal-free MRI contrast agent for glioblastoma diagnosis. This platform demonstrated efficient BBB crossing and tumor accumulation without toxicity in an orthotopic GL261 murine GBM mouse model, a significant advantage over gadolinium-based agents (Table 3). The dendrimer showed selective accumulation and longer retention in tumor tissue, enabling imaging over time frames of at least 2.5 hours, which is longer than typical gadolinium chelates [59].

2.4 Peptide-based and Other Dendrimers

Peptide-based dendrimers, along with a range of hybrid and synthetic dendrimer variants, like polyether-copolyester (PEPE) dendrimers, represent an expanding frontier in CNS-targeted nanomedicine (Figure 1). These dendrimers leverage biologically inspired monomers: amino acids, small peptides, and natural product mimetics, to impart intrinsic bioactivity and receptor recognition properties. Their modular nature also enables precise control over surface charge, hydrophobicity, and degradation profiles, key parameters for navigating the BBB [60, 61].

Amphiphilic peptide dendrimers functionalized with N1-alkyl tryptophan exhibited intrinsic antiproliferative effects against LN229, T98G, and U87MG glioblastoma cells. Notably, these dendrimers acted as both carriers and active drugs, partially inhibiting colony formation and scavenging reactive oxygen species *in vitro*. The dendrimers significantly reduced the clonogenic potential of GBM cells but did not achieve complete inhibition under the tested conditions [62]. Another bioinspired system employed H3/H6 peptide dendrimers (custom made lysine peptide dendrimer), mimicking motifs from the neurotrophic S100A4 protein, conjugated to gold nanostars. These constructs demonstrated neuroprotective effects in Alzheimer's and Parkinson's *in vitro* cell models, offering a dual role in therapy and targeted delivery [63].

Beyond peptides, carbosilane dendrimers and dendritic block copolymers have been explored for nucleic acid delivery and imaging. For instance, carbosilane dendrimers carrying siRNA against apolipoprotein E showed enhanced enzymatic stability and BBB transcytosis in neurodegenerative disease models *in vitro* [64]. Similarly, PEGylated gallic acid-triethylene glycol ester dendrimers delivered nucleic acid delivery in neural cells, optimizing cellular uptake without explicit BBB targeting [65].

Polyether-copolyester (PEPE) dendrimers have been studied as a promising candidate for CNS delivery. Second-generation PEPE dendrimers (D2 G2) demonstrate exceptional BBB-penetrating capabilities,

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achieving significant transcytosis rates across *in vitro* BBB models composed of murine bEnd.3 and human U373 MG cell cocultures [66]. Their unique architecture enables multiple internalization pathways, with clathrin- and caveolin-mediated endocytosis being predominant. Unlike traditional PAMAM dendrimers, PEPE systems combine the advantages of polyether flexibility with polyester biodegradability, resulting in enhanced biocompatibility and controlled release profiles [67].

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Box 1: Dendrimer Synthesis: Enabling Precision BBB Delivery

While this review focuses on BBB-crossing dendrimers, understanding synthesis approaches is crucial as they directly impact dendrimer properties critical for CNS delivery: size control, surface functionality, and batch-to-batch reproducibility.

Table B.1: Key Synthesis Methods for BBB-Relevant Dendrimers

Approach	Definition	Advantages for BBB Delivery	Limitations	Best for	References
Divergent	- Starts with a core molecule - Iterative addition of branching layers	- Scalable (G0-G4) - Low cost per gram	- Defects in ≥ G5 - Broad Polydispersity	Bulk PAMAM/PPI production	[68], [69]
Convergent	Presynthesized dendrons (branched subunits) are attached to a core molecule.	- High purity (95%) - Precise surface groups	- Limited to ≤ G4 - Expensive	Peptide/phosphorus dendrimers	[3]
Click Chemistry	- Quantitative and specific reactions in mild/biological conditions (e.g., CuAAC, thiol-ene)	- Bioorthogonal modifications - High yield	- Copper removal needed for CuAAC	Targeted RMT, ligand conjugation	[70], [71], [72]
Solid-Phase	- Dendrimer growth on a resine support - Iterative coupling/deprotection steps.	- Automated - Ideal for peptide dendrimers	- Low yields (30-70%)	GLP-grade theranostic agents	[73], [74], [75]

Although each synthesis method offers unique advantages, scaling dendrimer production for clinical use introduces additional challenges, particularly when maintaining precise control over molecular features critical for BBB navigation. Manufacturing bottlenecks such as purification complexity, structural defects, and toxicity must be addressed to ensure therapeutic efficacy and safety. ***Table B.2*** *summarizes these major challenges and the strategies being developed to mitigate them:*

Table B.2:

Challenge	Impact	Mitigation Strategies
Purification	Structural defects reduce efficacy in therapeutic settings.	Hybrid synthesis, in-line chromatography, real-time SEC monitoring [76], [77].
Structural Defects	Higher generations (≥G5) exhibit 10–30% imperfections [78].	Preactivated monomers (e.g., NHS esters), stoichiometry optimization [79], [80].
Cost	PAMAM G5 costs >$500/g, ~10× G2 cost.	Bulk reagents, flow-based synthesis, automated solid-phase systems [81], [82].
Reproducibility	Batch-to-batch variability (PDI >1.2) complicates scale-up and approval [83].	In-line NMR monitoring, GMP protocols, QbD (Quality-by-design) implementation [84],[85].

Looking ahead, emerging innovations such as hybrid synthetic strategies (e.g., divergent core generation with convergent ligand conjugation), continuous flow reactors for batch reproducibility, and AI-guided synthetic optimization are poised to overcome these bottlenecks. These trends will be critical for achieving the stringent control over dendrimer architecture necessary for safe and effective BBB-targeted therapeutics.

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3. Mechanisms of BBB Crossing by Dendrimers

The BBB, formed by endothelial cells tightened up with tight junctions, astrocyte end-feet, and pericytes, presents both physical and biochemical barriers to drug delivery. Dendrimers traverse the BBB via multiple pathways, influenced by generation, surface chemistry, and functionalization (Figure 3, Table 3).

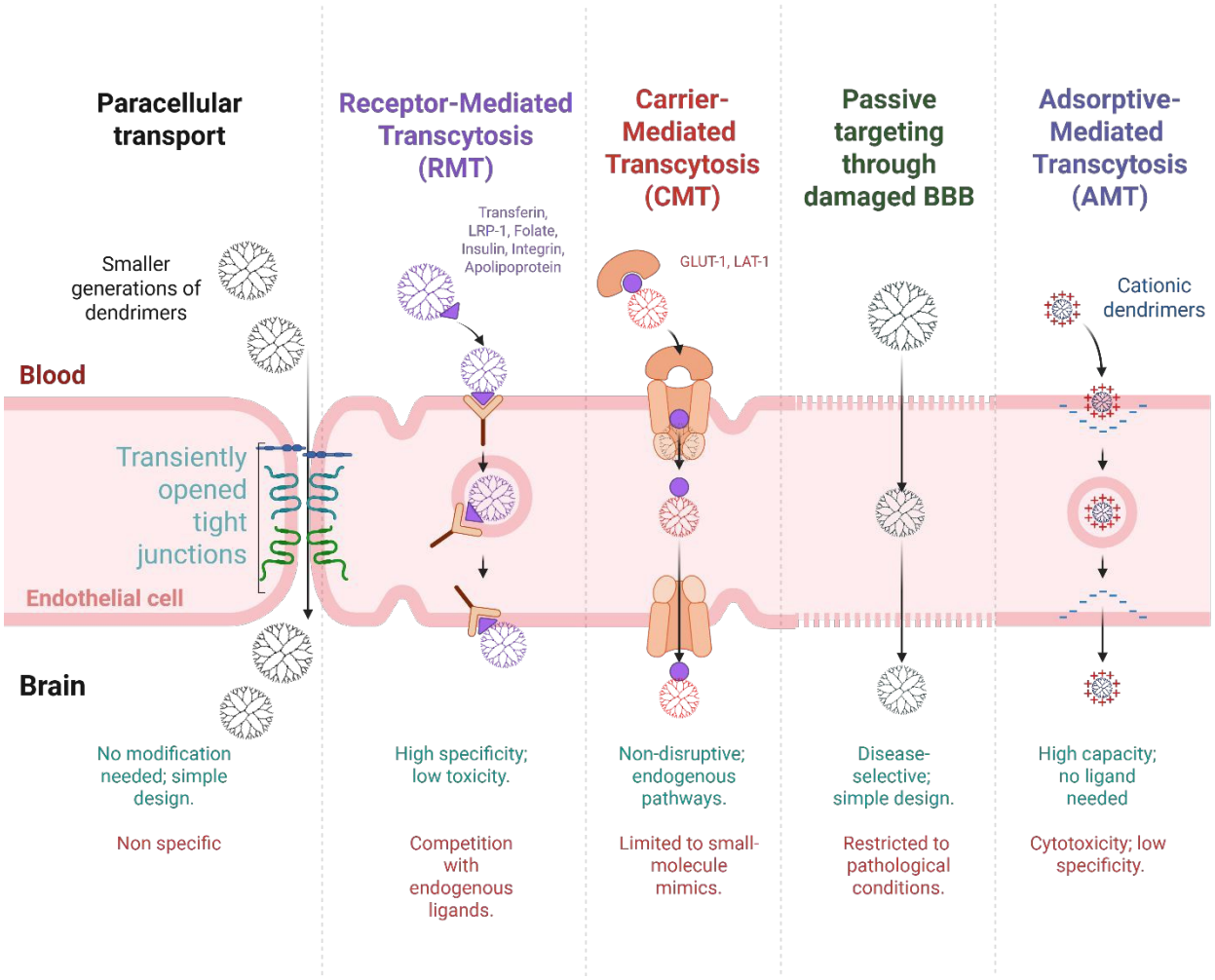

*Figure 3: Mechanisms of blood–brain barrier (BBB) crossing by dendrimers. Dendrimers may traverse the BBB through multiple pathways: (1) Paracellular transport, involving transient opening of tight junctions, typically for low-generation dendrimers; (2) **Receptor-mediated transcytosis (RMT)** via functionalization with ligands targeting endothelial receptors such as transferrin, LRP1, folate, insulin, integrin, and apolipoprotein; (3) **Carrier-mediated transcytosis (CMT)** using substrate analogs to engage transporters like GLUT1 and LAT1; (4) **Passive targeting**, exploiting BBB disruption in pathological conditions such as neuroinflammation or glioma; and (5) **Adsorptive-mediated transcytosis (AMT)** through electrostatic interaction of cationic dendrimers with the negatively charged luminal surface. Created with Biorender.*

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3.1 Adsorptive-Mediated Transcytosis (AMT)

AMT is one of the most widely reported pathways for cationic dendrimers such as PAMAM, PPI, and phosphorus dendrimers. PAMAM and PPI dendrimers, primary and tertiary amines at the periphery, offer high positive charge density, enhancing adhesion to the brain capillary endothelial cells (BCEC) membrane [47], [86]. Their negatively charged components are predominantly sialoglycoproteins and heparan sulfate proteoglycans (HSPGs), particularly glypicans and syndecans, which provide anionic carboxyl and sulfate groups mediating dendrimer binding and subsequent endocytosis [87]. These interactions trigger non-specific uptake via membrane invagination and subsequent exocytosis via vesicular transcytosis (Figure 3) [87]. Cationic dendrimers such as PAMAM-G2 or G3 exploit this mechanism, by the virtue of their small size (approximately 2–3 nm) and high surface charge density facilitate strong adsorption to endothelial membranes, promoting transcytosis. For example, a G2 PAMAM dendrimer conjugated with citicoline and albumin achieved BBB penetration by AMT in ischemic stroke models, where the cationic surface enabled binding to the negatively charged glycocalyx, followed by vesicular transcytosis into the brain parenchyma [46]. Notably, AMT is distinct from receptor-mediated transcytosis as it does not saturate easily, allowing high-capacity transcytosis [88].

As already mentioned, the downside of using cationic dendrimers is their inherent toxicity. Upon binding, highly charged cationic dendrimers disrupt the anionic phospholipid bilayer of cellular membranes by inducing lipid rearrangement, forming transient or permanent nanopores, and disturbing membrane fluidity [89]. This process causes direct membrane lysis or destabilization, especially at high concentrations or with higher-generation dendrimers (G4-G7) [90]. The disruption of the plasma membrane can trigger calcium influx, mitochondrial membrane potential collapse, and release of cytochrome c, initiating apoptotic pathways [91]. Furthermore, endosomal escape, often mediated by the "proton sponge effect" due to tertiary amines in PAMAM cores, can rupture endosomal membranes, leading to leakage of lysosomal enzymes and cytosolic oxidative stress [92]. To counter this, achieving an active balance between the cationic and anionic charges on dendrimer surface is important.

Phosphorus dendrimers, especially hydroxyl-terminated variants, show reduced charge density but can be engineered with amine partial peripheral coverage to engage AMT selectively while preserving biocompatibility [93]. Another strategy is to precisely functionalize dendrimers with cell-penetrating peptides (CPPs), such as TAT or polyarginine, thereby enabling both electrostatic and proteoglycan-specific interactions [94].

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3.2. Receptor-Mediated Transcytosis (RMT)

RMT is a highly selective and energy-dependent transcytosis process enabling dendrimer-based nanocarriers to traverse the BBB via specific ligand–receptor interactions. This mechanism exploits the expression of surface receptors on the luminal side of brain endothelial cells, triggering clathrin- or caveolae-mediated endocytosis and transcellular trafficking without disrupting the tight junctions of the BBB (Figure 3). Thanks to their monodisperse architecture and multivalent surface chemistry, ligand-functionalized dendrimers often exhibit cooperative binding and receptor-mediated uptake. Below are the main receptors reported for dendrimer delivery through BBB.

3.2.1. Transferrin Receptor (TfR)

TfR is one of the most extensively studied RMT pathways at the BBB. It facilitates the internalization of transferrin-bound iron and has been widely targeted using both native ligands and anti-TfR antibodies [95]. For example, transferrin conjugated G4 PAMAM dendrimers were utilized to deliver tamoxifen. The surface was modified with polyethylene glycol (PEG) to enhance its stability and circulation time, while the conjugated transferrin served as an active targeting ligand. The study demonstrated enhanced BBB crossing, with the Tf-dendrimer-tamoxifen complex exhibiting a transcytosis ratio of 6% in 3 hours, a statistically-significant increase compared to the Tf-only carrier (4.9%) and non-targeted carriers (4.6%). Tf-dendrimer reduced the IC50 of tamoxifen in C6 glioma cells from 6.91 μg/mL to 3.22 μg/mL, as compared to free tamoxifen, demonstrating a 2.15-fold improvement in anticancer activity. The superior performance of the nanocarrier was attributed to its ability to not only deliver tamoxifen but also to inhibit drug efflux pumps, thereby overcoming multidrug resistance. However, a major limitation persisted due to competition with high endogenous levels of transferrin in the bloodstream, which can saturate TfR and reduce the efficiency of the nanocarrier's targeting and subsequent transcytosis across the BBB [96].

3.2.2. Low-Density Lipoprotein Receptor-Related Protein 1 (LRP1)

LRP1 is highly expressed in endothelial cells and is upregulated under neuroinflammatory conditions. Angiopep-2 is a 19-amino-acid peptide that exhibits high affinity for LRP1 [83]. An Angiopep-2-conjugated PAMAM dendrimer was used to deliver doxorubicin. In a mouse model of glioma, the brain-to-blood ratio of the Angiopep-2-dendrimer-doxorubicin complex was found to be 2.5 times higher than that of free doxorubicin. This enhanced delivery led to a significant increase in anti-tumor efficacy, with the dendrimer complex achieving a 6-fold increase in tumor growth inhibition compared to the free drug [97, 98]. In

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another study, lactoferrin conjugated G3 PAMAM dendrimers were used to deliver memantine hydrochloride in male Sprague-Dawley rats. Lactoferrin, a natural ligand for LRP1, was chosen for its high affinity for the receptor. The dendrimer platform was essential for encapsulating the drug and facilitating its passage across the BBB. The study demonstrated a remarkable improvement in drug brain delivery. The brain-to-blood ratio of memantine delivered by the Lf-dendrimer system reached 1.95, significantly higher than 0.81 observed for free memantine. This led to a substantial 3.27-fold increase in drug concentration in the brain at the maximum concentration compared to the free drug [99].

3.2.3. Folate Receptor (FR)

Although expressed at low levels in normal brain endothelium, FR is significantly upregulated in several brain tumor types [100]. Folic acid-conjugated G5 PAMAM dendrimers have been used for selective RMT into tumor tissue, offering potential for enhanced doxorubicin treatment. This nanocarrier was conjugated with folic acid for tumor-specific targeting and modified with borneol, a natural product that performs a dual function: reducing dendrimer toxicity and boosting BBB penetration. In an in vitro BBB model using bEnd.3 cells, the borneol-modified dendrimer showed a permeability coefficient (Papp) of 8.63×10^{-7} cm/s, which was 1.8-fold higher than that of the non-modified dendrimer (Papp of 4.76×10^{-7} cm/s). This enhanced penetration was attributed to borneol's ability to modulate tight junctions and inhibit drug efflux pumps like P-glycoprotein. [101].

3.2.4. Insulin Receptor (IR)

The IR plays a critical role in CNS glucose regulation and is constitutively expressed at the BBB. While native insulin is rapidly cleared and poses hypoglycemia risks, humanized monoclonal antibodies (e.g., HIRMAb) targeting IR have been developed as RMT vectors with minimal interference in glucose homeostasis [102]. Fusion proteins incorporating HIRMAb and therapeutic enzymes or antibodies (e.g., α-L-iduronidase, anti-Aβ scFv) have demonstrated effective CNS delivery and are currently in preclinical and clinical development for conditions such as Hurler's syndrome. In a preclinical study in rats, this HIRMAb-IDUA fusion protein demonstrated a 30-fold greater brain uptake compared to the unconjugated enzyme. [103].

3.2.5. Integrin Receptors

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Integrins, particularly $\alpha_v\beta_3$, are overexpressed in the tumour vasculature and angiogenic endothelium, making them attractive targets for dual tumour and BBB targeting [104]. RGD peptides, especially cyclic derivatives like c(RGDfK), have been conjugated to dendrimers (for example, G2 PAMAM) to facilitate selective uptake in gliomas and MR/CT imaging of metastatic lesions thanks to loaded manganese chelates. In vitro, the RGD-conjugated dendrimer demonstrated a significantly higher affinity and uptake (10-20 fold) in $\alpha_v\beta_3$-positive glioma cells compared to $\alpha_v\beta_3$-negative cells, confirming the high specificity of the RGD peptide. This selective uptake translated to superior in vivo imaging ability. In a mouse model of glioma, the MR/CT imaging signal intensity from the RGD-dendrimer-manganese chelate complex in the tumor tissue was 3.5 times higher than in the surrounding healthy brain tissue. The increased signal-to-noise ratio allowed for the more precise visualization of tumor margins and metastatic lesions. [105].

3.3 Carrier-Mediated Transcytosis (CMT)

CMT across the BBB leverages endogenous solute carrier (SLC) proteins that facilitate the influx of essential nutrients such as glucose, amino acids, and vitamins into the CNS. These transporters are highly expressed on the luminal membrane of brain endothelial cells and present an attractive target for nanocarrier-based drug delivery systems, including dendrimers. Unlike receptor-mediated pathways that rely on ligand-receptor binding, CMT is substrate-specific and often saturable, making the selection and design of transporter-compatible ligands a critical aspect of dendrimer functionalization [106].

Glucose Transporter 1 (GLUT1) is the primary hexose transporter at the BBB, responsible for the facilitated diffusion of D-glucose into the brain. It is constitutively expressed on both luminal and abluminal surfaces of endothelial cells, making it a prime target for nanoparticle delivery [107]. G4 PAMAM dendrimers conjugated with glucose facilitates GLUT1-mediated endocytosis, allowing for the preferential accumulation of therapeutic payloads in seizure-prone neuronal circuits. In a pilocarpine-induced seizure model, intranasal delivery of glucose-functionalized PAMAM (100 µg in 10 µL) during ongoing seizures produced detectable fluorescence in the neuronal layers of the olfactory bulb, cortex, and hippocampal CA1 region within 4 hours. Confocal microscopy revealed up to 10-fold higher fluorescence than with free G4 PAMAM dendrimers, along with seizure attenuation. This suggests that the glucose-functionalized dendrimer is able to bypass or cross the BBB via the intranasal route and selectively localize in hyperexcitable neurons [108]. In another study, 2-deoxy glucose conjugated G4 PAMAM dendrimers were used to deliver pioglitazone, a neuroprotective agent, directly against traumatic brain injury (TBI). In vivo biodistribution studies showed that, following intraperitoneal administration, dendrimer construct

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accumulated in the injured hemisphere at levels up to ~7% of the injected dose within 1 h, compared to ~0.5–1% in the contralateral non-injured hemisphere and <0.5% in sham controls representing more than a 7- to 10-fold increase in BBB permeation into injured tissue. Confocal imaging confirmed robust neuronal colocalization in perilesional areas, with uptake persisting for at least 24 h, though at lower levels (~3% of injected dose in injured vs. ~0.2% in sham). Therapeutically, animals receiving dendrimer–pioglitazone exhibited a significant reduction in microglial activation (and improved neuronal survival compared to both saline and free pioglitazone treatment. These findings indicate that glucose-modified dendrimers can achieve markedly enhanced BBB penetration and selective accumulation in injured brain regions after TBI, thereby increasing local drug exposure while potentially reducing systemic toxicity [109]. However, the TBI model likely involved extensive tissue damage and severe BBB disruption, which may have exaggerated the observed accumulation. This limitation should be considered when extrapolating these findings to conditions with intact or moderately compromised BBB integrity.

L-type amino acid transporter 1 (LAT1) is a high-affinity, sodium-independent amino acid transporter that primarily facilitates the transcytosis of branched and aromatic amino acids such as phenylalanine, tyrosine, and leucine [110]. LAT1 is not only highly expressed at the BBB but is also overexpressed in various brain tumors, offering a dual-targeting opportunity [111]. In a SPECT scintigraphy study using tumor-bearing Wistar rats, phenylalanine-functionalized G2 PAMAM dendrimers (G2–Phe) demonstrated markedly enhanced brain uptake compared to unmodified G2 dendrimers. One hour after intravenous injection of the radiolabeled constructs (^{99m}Tc-G2 or ^{99m}Tc-G2–Phe) into rats bearing C6 glioma xenografts, SPECT/CT imaging revealed higher accumulation of the G2–Phe in the tumor-bearing brain regions. Quantitative analysis showed that the mean radioactive count for G2–Phe in the brain was ~7,279 counts, compared to ~4,595 counts for unmodified G2, representing an average ~1.58-fold increase in BBB penetration. The enhancement was consistent across animals, with the G2–Phe/G2 ratio ranging from 1.59 to 1.67 [112].

Monocarboxylate transporters (MCTs), particularly MCT1–4, facilitate the proton-coupled transcytosis of lactate, pyruvate, and short-chain fatty acids, and are notably upregulated under conditions of metabolic stress, such as gliomas or ischemia [113]. Similarly, choline transporters, including the high-affinity CHT and the sodium-independent CTL1, are involved in acetylcholine biosynthesis and are expressed at the BBB [114]. Dendrimers conjugated with choline derivatives can exploit this route for enhanced delivery to cholinergic neurons, especially in glioma [115].

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3.4 **Passive Targeting Through Damaged BBB**

The "BBB window" for passive targeting, when the BBB is altered, is governed by nanoparticle size (<100 nm optimal)[36], surface charge (neutral/anionic preferred)[116], and temporal dynamics, with peak permeability occurring 24–72 hours post-injury [117]. Albumin, a natural marker of BBB disruption, provides critical insights: its 7-nm hydrodynamic diameter and gp60-mediated transcytosis set a benchmark for nanoparticle design [118, 119]. An example of this strategy was demonstrated by a dual-stage delivery system for glioblastoma treatment. The team conjugated G2 PAMAM dendrimers with albumin, creating a biomimetic carrier that was further encrusted with doxorubicin-loaded PLGA nanoparticles. This innovative design capitalized on albumin's natural transcytosis mechanisms while leveraging the dendrimer's multivalency and PLGA's drug encapsulation capacity. The results showed that the albumin-dendrimer-PLGA complex achieved 10-fold higher permeation across a bEnd.3 BBB model compared to free doxorubicin, and 2-fold greater permeation than PLGA nanoparticles alone [120]. In neuroinflammatory or ischemic conditions, the BBB becomes locally permeable. Hydroxylated dendrimers (e.g., 90-OH PAMAM) exploit this disruption for passive targeting (Figure 3). Their accumulation in activated microglia and astrocytes allows site-specific delivery without the need for external ligands, as demonstrated in cerebral palsy and COVID-19-related neuroinflammation models using OP-101 [29, 121].

Though debated, smaller dendrimers (G0–G2) may occasionally traverse the BBB via transient tight junction opening or size-mediated diffusion. Some in vitro studies with PAMAM-G1 and G2 suggest enhanced permeability through compromised tight junctions in disease models, but this remains mechanistically less understood [121],[122].

Overall, the mechanism of BBB traversal is not only determined by the dendrimer's structure but also by the disease context and the specific cellular and molecular environment. The ability to tailor dendrimers for a particular route through surface charge, ligand attachment, or stimulus-responsive behavior makes them uniquely suited for the complex demands of CNS drug delivery and diagnostics.

4. Current Applications of Dendrimers in BBB Delivery

The versatility of dendrimers in traversing the BBB has enabled their application across a spectrum of neurological disorders, ranging from acute conditions (e.g., stroke) to chronic neurodegenerative diseases (e.g., Alzheimer's) and aggressive brain tumors. Table 3 illustrates key studies, reporting the dendrimer design, functionalization, drug and disease models.

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Table 3: Current applications of dendrimers in BBB delivery for neurological disorders, highlighting dendrimer types, surface modifications, therapeutic cargo, disease targets, and preclinical models.

Dendrimer Type	**Surface Modification / Ligand**	**Drug / Cargo**	**Disease Target**	**BBB Model (In Vitro / In Vivo)**	**Main outcomes**	**Ref**
PAMAM G2	Cationized albumin	Citicoline (CIT)	☐Stroke	bEnd.3 cells; PC-12 hypoxia model	Three-fold higher permeation in vitro.	[46]
PAMAM G2	DOTA-Gd + GCN5 inhibitor + ICG	Imaging/therapy	●☐ Glioma	Astrocytes + hCMEC/D3 cells	~50% crossing rate	[123]
PAMAM G2	RGD peptide + AuNPs / Mn^{2+}	Imaging probe	● ☐ Glioblastoma (GBM)	Orthotopic glioma mice	1.4× MR S/N and 1.5× CT signal enhancement in glioma (targeted vs. non-targeted) Significant Au accumulation in brain at 45 min, 12 h, 24 h post-injection ($p < 0.01$).	[105]
PAMAM G2	Albumin	Doxorubicin (DOX)/ PLGA nanoparticle	● GBM	bEnd.3 cells	~10-fold increase in permeation (dendrimer vs free drug)	[120]
PAMAM G2/G3	Streptavidin adapter	None	☐ BBB mechanism studies	PBECs + bEnd.3 + neurons/astrocytes	~0.44 µg/g brain delivery after injection in healthy mice. Up to 38% transcytosis across in vitro brain barrier model	[40]
PAMAM G3	PMPC surface modification	Doxorubicin (DOX)	● GBM	U-87; glioma mice	Strong brain tumor accumulation up to 24 h; signal intensity in brain ~2× higher than PEGylated control	[124]
PAMAM G3	Lactoferrin (Lf)	Memantine (MEM)	☐ Alzheimer's disease (AD)	Rats	MEM-PAMAM-Lf increased brain delivery by ~2.4× compared to MEM alone and ~1.8× compared to PAMAM-MEM	[99]
PAMAM G4	PEGylated + Rhodamine B	Imaging probe	☐☐ Ischemic stroke	Astrocyte–bEnd.3 coculture; mice	~10 times increase in fluorescence intensity	[47]
PAMAM G4	Amine-terminated + nanodiamonds	Cabazitaxel (CTX)	● GBM	U87 cells	10× lower IC50 for NPC vs. crystalline CTX on U87 cells. 4× higher cellular uptake of NPC	[125]
PAMAM G4	2-Deoxyglucose (2DG)	Pioglitazone	☐ Traumatic brain injury (TBI)	CATH.a neurons; rats	~6% of injected dose was found in the brain cortex.	[109]
PAMAM G4	Tocopheryl PEG succinate (TPGS)	Piperine	☐ AD	SH-SY5Y cells; rats	2.2 ± 0.37 µg/g PIP content was observed in the brain, compared to the 0.4 ± 0.10 µg/g of PIP alone	[126]
PAMAM G4	Glucose	Anticonvulsant	☐ Epilepsy	Neurons; seizure mice	~100× higher Cy5 signal in contralateral CA1 neurons for GD2 vs PAMAM-OH after seizure induction.	[127]
PAMAM G4	Transferrin (Tf) + Tamoxifen (TAM) + PEG	Doxorubicin (DOX)	● Glioma	BMVECs; C6	~2x increase in BBB permeation	[96]
PAMAM G4	Angiopep-2 + EGFR peptide (EP-1) + PEG	Doxorubicin (DOX)	● GBM	HBMEC; SCID mice	~3× BBB transcytosis over free DOX.	[97]
PAMAM G4/G4.5	Amine/carboxylate terminals	Carbamazepine (CBZ)	☐ AD	N2a cells; zebrafish	CBZ solubility in water (~0.5 mM) increased ~3× when complexed with DG4.0 or DG4.5 at 1:150 molar ratio.	[128]

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PAMAM G5	Folic acid	Burneol (BO), doxorubicin	● Glioma	HBMECs; rats	≈ 5.6× increase in tumor targeting vs BO-PAMAM	[101]
PAMAM G5	Angiopep-2 + PEG	pORF-hTRAIL (gene therapy)	◉ ● Glioma (gene therapy)	C6 cells; ICR mice	Brain/tumor accumulation: PAMAM-PEG-Angiopep > PAMAM-PEG > PAMAM.	[98]
PAMAM G5	Glutathione-sensitive linker	siRNA (anti-GFP)	◉ ● GBM (gene therapy)	CX3CR-1GFP mice	~64% GFP knockdown in TAMs at 24 h post-injection (free siRNA: ~53%).	[48]
PAMAM G5	Angiopep-2 + GE11 (EGFR targeting)	NIR783 / Gd^{3+} DTPA	● Brain metastases	Nude mice	Carrier crossed an intact BBB in TNBC brain metastasis model, giving 64.2 % binding to EGFR-high cells in vitro and detectable T1/NIRF brain signal within 1–2 h post-injection, before Gd-DTPA leakage.	[49]
PAMAM G5/G3 Core–Shell	β-cyclodextrin core + adamantane/dermorphin /RGD shell	Cu(II) (CDT therapy)	● GBM	HBMECs; glioma mice	BBB penetration confirmed by brain Cu accumulation up to 24 h.	[129]
PAMAM-PIP-TPGS	Piperine + TPGS	Piperine	☐ AD	SH-SY5Y cells	ROS reduced to 15.21% (free PIP: 48.5%). Apoptosis reduced from 38.2% to 12.36%. Disaggregated Aβ1–42 fibrils effectively.	[130]
PPI G5.0	Concanavalin A / sialic acid / glucosamine	Paclitaxel (PTX)	● Brain tumors	U373MG cells, mice	Sialic acid–PPI accumulates in brain up to 573.9 μg/g at 8 h, ~54.65× higher than plain PPI, ~20–32× higher than free PTX.	[53]
Phosphorus (AK123)	Fibronectin (RGD motif)	None	☐ Parkinson's disease (PD)	bEnd.3 - BV2 microglia coculture; Mice	≈1.8× higher BBB crossing	[58]
Phosphorus (AK128)	M1m macrophage membrane-camouflage + anti-PD1	None (immune therapy)	● Glioma	bEnd.3; C6 mice	Carrier showed 34.36% penetration in vitro BBB model ($p < 0.001$) and highest in vivo brain fluorescence among groups, peaking at 6 h; brain glioma uptake markedly greater than Cy5.5-IgG and uncoated AK128. Blood half-life extended to 1.076 h vs 0.775 h (uncoated) and 0.7446 h (free IgG), likely from immune evasion by M1m coating.	[131]
PPH G3	48 PROXYL radicals	MRI contrast agent	● GBM	GL261 mice	Achieved RCE (Relative Contrast Enhancement) 237 ± 40% ex vivo (similar to Gd-DTPA at 232 ± 29%) at only 1.25 nmol injected per site. In vivo (GL261 glioblastoma), 0.025 mmol/kg dose yielded 126% RCE at 6 min, maintained 121% at 60 min far slower washout than Gd (which dropped to ~125% in 30 min).	[59]
Peptide (H3/H6)	Gold nanostars / neuroprotective peptides (AuNS)	None	☐ AD/PD	SH-SY5Y cells; primary neurons	In a triple co-culture BBB model, H3-AuNS crossed with 17 % efficiency vs H3-AuNP at 11%. Previous AuNS studies reached ~20% without targeting ligands and ~40% with BBB-targeting	[63]

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					molecules, suggesting room for optimization.	
PEG-GATGE	Dendriplexes	siRNA	◍ ☐ Neurodegeneration	ND7/23; HT22 neurons	Fast neuronal uptake: ~89% (PNS) and ~84% (CNS) Cy5+ cells within 0.5 h. Complete uptake (~100% positive cells) within 2 h. The carrier also avoided lysosomal entrapment.	[65]
Polyester G3	Dopamine chelation	^{99m}Tc tracer	☐ Biodistribution studies	HEK-293/PC12; mice	10% injected dose/g in brain at peak, with highest accumulation in olfactory tract and substantia nigra within 30 min. Targeting attributed to dopamine moiety binding to D1 dopamine receptors along nigrostriatal pathway.	[132]
Carbosilane G3/G4	PEGylated	siRNA (ApoE targeting)	◍ ☐ Neurodegeneration (gene therapy)	HBEC-5i cells	G3Si PEG6000 dendrimer formed the smallest, most stable siRNA complexes (~14 nm), showed the highest binding affinity, and had the lowest cytotoxicity in human brain endothelial (HBEC-5i) cells, making it the most promising candidate for future BBB delivery studies.	[64]
Polyether G2 (PEPE)	Rhodamine B	Imaging probe	☐☐ BBB mechanism studies	bEnd.3 + U373MG coculture	Papp of 40 × 10^{-6} cm/s achieved in vitro. Uptake mainly via clathrin- and caveolin-mediated endocytosis (47–73% and 49–69% inhibition by pathway-specific inhibitors), with minimal fluid-phase endocytosis.	[66]
Heparan Sulfate Mimetic (Tet-29)	BODIPY-labeled	None	☐ Multiple sclerosis (MS)	bEnd.3; EAE mice	Tet-29 significantly reduced inflammatory BBB infiltration in EAE, lowering brain $CD4^+$ T cells by ~65%.	[133]

Symbol	Application
●	Tumors (glioblastoma, brain tumors)
☐	Neurodegenerative diseases (AD, PD, MS)
☐	Stroke/Trauma/Epilepsy
◍	Gene therapy / siRNA delivery
☐	General BBB studies, biodistribution
☐	Imaging studies.

5. Clinical Translation

Dendrimer-based nanomedicines have progressed from bench to bedside, with several platforms now in clinical trials or approved for neurological, oncological, and infectious diseases. From a regulatory

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perspective, dendrimers are evaluated under frameworks applicable to nanomedicines and polymer therapeutics (Box 2). For instance, ^{18}F-OP-801, a hydroxyl G4 PAMAM with a ^{18}F PET tracer, is taken up by active microglia and macrophages, and can detect neuroinflammation at lower levels and at early stages of the disease progression. It is currently going to Phase I/II study, after preclinical studies demonstrated its ability to penetrate the BBB and to accumulate in brain areas with inflammation, such as the cortex, brain stem, and olfactory bulb, as shown in LPS-challenged mice [33, 134]. The translational gap exists predominantly because of the toxicity issues relevant to dendrimers. Extensive study has been undertaken in the field to understand the toxicity of dendrimers, specially the commercially available PAMAM dendrimer (Figure 4).

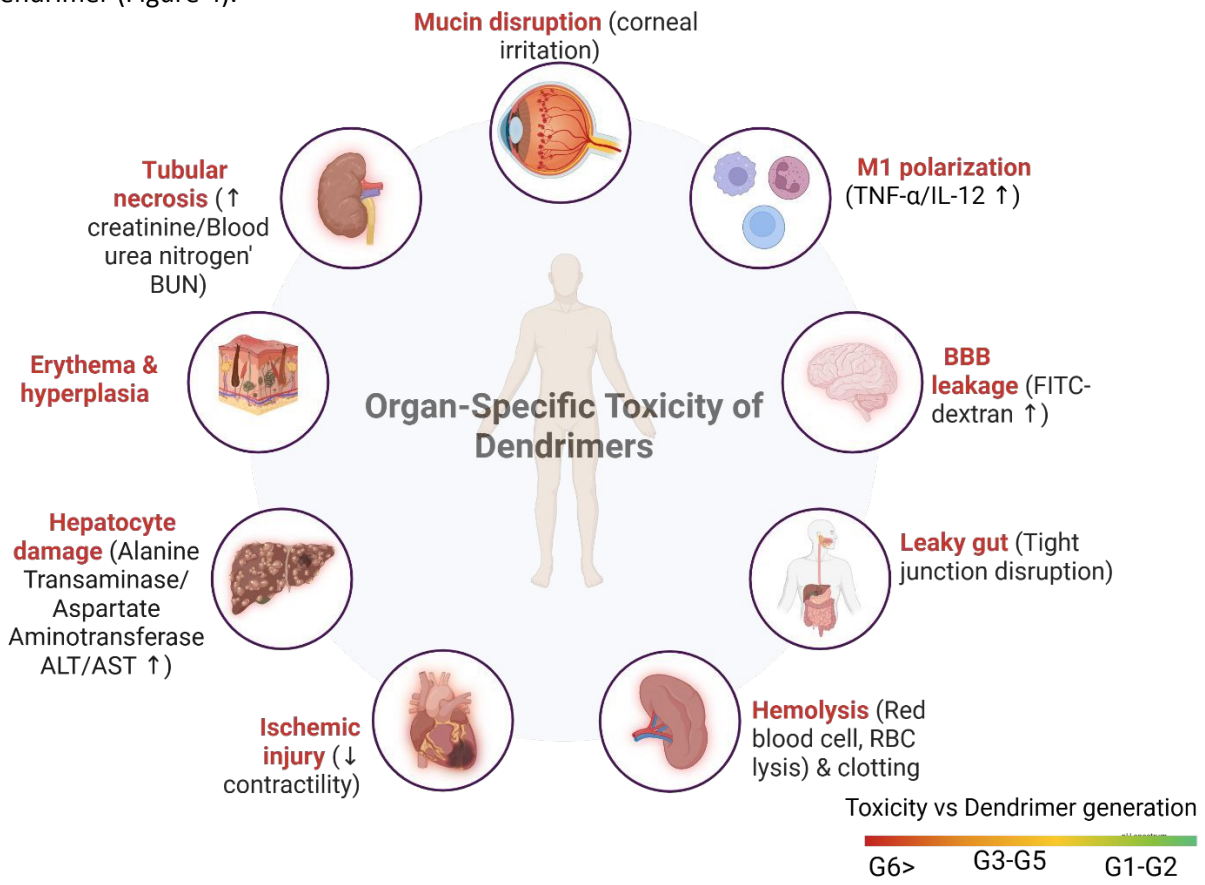

Figure 4: Schematic overview of organ-specific toxicities associated with dendrimer administration. Created with Biorender. Refer to [134-155].

The limited clinical translation of dendrimer-based nanotherapeutics stems from a combination of biological and technical challenges. First, our understanding of the dynamic and heterogeneous nature of the BBB across neurological disorders is still incomplete. The current binary classification of the BBB as either "inflamed" or "non-inflamed" fails to capture the heterogeneity of barrier dysfunction across

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neurological diseases [156]. Emerging evidence shows that pathologies like multiple sclerosis, Alzheimer's, stroke, aging, and brain tumors each exhibit distinct patterns of BBB dysfunction, involving differences in tight junction disruption [157], basal lamina integrity [158], receptor expression [159], and glycocalyx alterations [160]. This diversity profoundly impacts the rational design of dendrimer nanocarriers, as particle size, charge, and targeting moieties must align with disease-specific BBB pathophysiology. Yet, current ligand selection remains largely empirical, hindered by insufficient mapping of biomarker dynamics and receptor profiles during disease progression. For instance, transferrin receptor (TfR) expression increases during neuroinflammatory diseases, a variability often overlooked in targeting strategies [161]. Another example could be the decrease of active efflux transporters, like ABCB1, during glioblastoma [162].

Second, technical barriers persist in dendrimer synthesis and characterization. Unlike conventional nanoparticles, dendrimer architectures become increasingly complex with higher generations, introducing defects such as incomplete branching due to steric hindrance [68] (Box 1). Analytical challenges also limit precise determination of three-dimensional structural integrity, ligand conjugation ratios, and intra-dendrimer drug distribution. These complexities create formidable hurdles for scalable manufacturing and regulatory approval, as standardized frameworks for evaluating nanotherapeutics remain underdeveloped compared to small molecules or biologics (Box 2).

However, even when manufacturing and regulatory-readiness hurdles are overcome, translation to the clinic introduces a new set of obstacles, particularly in CNS diseases, where the selection of appropriate clinical trial endpoints is itself a highly complex process. Unlike trials for many other conditions, CNS studies often rely on endpoints that capture how patients “feel or function,” making standardized, validated scales critical [163]. The end points vary depending on the target condition. In Alzheimer’s disease, primary endpoints often rely on composite measures that capture both cognitive function and the patient’s ability to perform daily activities. A widely used example is the Alzheimer’s Disease Assessment Scale–Cognitive Subscale (ADAS-Cog), which is frequently complemented by the Alzheimer’s Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) scale to provide a more comprehensive evaluation of treatment effects on daily functioning [164]. On the other hand, glioma trials focus on survival and tumor progression because the disease is directly life-threatening. Overall Survival (OS) is the gold standard primary endpoint for large Phase III trials, as it represents an objective and definitive measure of a treatment's benefit [165]. PD trials focus on both symptomatic relief and slowing disease progression. The most widely used endpoint is the Unified Parkinson's Disease Rating Scale (UPDRS), a

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clinician-rated scale that assesses motor and non-motor symptoms. Part III of the UPDRS, which evaluates motor function, is a common primary endpoint for trials testing symptomatic treatments [166].

The FDA and other regulatory a provide specific guidance on what constitute a valid endpoint for different CNS conditions, emphasizing the importance of endpoints that are both statistically robust and clinically meaningful to patients.

When examining the translation of OP-101 and its diagnostic analogue ^{18}F-OP-801, several factors may underpin their relative success in reaching clinical evaluation. Both are based on generation-4 hydroxyl-terminated PAMAM dendrimers, which are neutral in charge, substantially reducing cytotoxicity and nonspecific interactions [167] compared to cationic amine-terminated counterparts. These dendrimers exploit a pathology-driven targeting mechanism, selectively accumulating in activated microglia and astrocytes within regions of neuroinflammation, bypassing the need for ligand receptor targeting strategies that may vary between diseases and patients. The therapeutic payload of OP-101 (N-acetylcysteine) already has extensive human safety data and its covalent conjugation to the dendrimer improves solubility, brain penetration, and retention in inflamed CNS regions [168, 169]. Importantly, the chemistry is reproducible at GMP scale, backed by comprehensive toxicology and pharmacokinetic packages, which facilitated regulatory progression [170].

This starkly contrasts with the fate of many other nanocarriers. For instance, the case of Starpharma's VivaGel® (SPL7013), a lysine-based dendrimer designed for topical microbicide use, highlights important safety considerations: although early data were promising, clinical trials revealed that repeated use could cause mild, reversible mucosal irritation and local inflammation [171]. These findings ultimately limited its efficacy as a preventive product, underscoring how dendrimer-specific safety issues can impact even non-CNS applications. For brain delivery, these hurdles are magnified. Cationic PAMAM or PPI dendrimers, for example, demonstrated compelling efficacy in rodent models of glioblastoma (Table 3) but were universally shelved preclinically due to insurmountable systemic toxicity, including hemolysis [150] and hepatotoxicity [172]. Similarly, sophisticated "designer" dendrimers conjugated to complex targeting ligands (e.g., peptides for receptor-mediated transport) have foundered not on scientific merit, but on the impracticality of developing a scalable, regulatory-ready manufacturing process for such a chemically intricate product [173, 174]. Thus, the transition from compelling animal data to a viable human medicine ultimately hinges on overcoming these foundational barriers of safety, scalable production, and regulatory characterization, challenges that have consigned numerous promising dendrimer platforms to the "valley of death."

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Box 2: Regulatory Classification of Dendrimers in Pharmaceutical Products

The regulatory status of dendrimers depends on their function: as drugs (APIs), carriers (excipients), or hybrid systems [44]. This box outlines decision criteria, approval routes, and relevant guidance documents shaping their clinical translation.

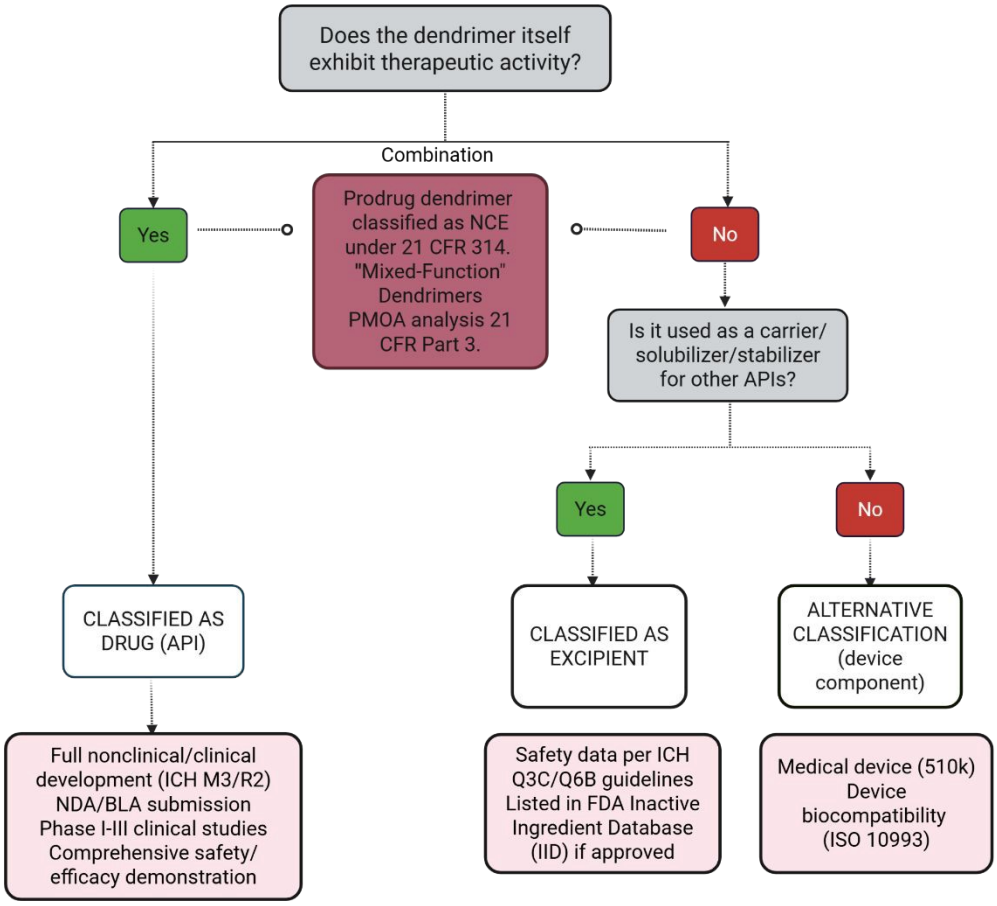

Figure B2.1: Figure: Regulatory flowchart for dendrimer classification based on therapeutic intent, delivery function, or hybrid mechanisms.[175-178], NCE = New chemical entity; PMOA = Primary mode of action; CFR = Code of Federal Regulations; NDA/BLA = New drug application/ Biological license application;

Summary of Regulatory Requirements Based on Dendrimer Role in Formulation

Aspect	*As Drug (API)*	*Mixed Drug/Excipient*	*As Excipient*
Safety Data	*Full good laboratory practices (GLP) toxicity studies (ICH S6(R1)) + immunogenicity*	*• API-like toxicity for active scaffold • Excipient-level testing for carrier function*	*Biocompatibility (ISO 10993)*

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CMC Requirements ((Chemistry, Manufacturing, Controls)	*Full characterization (ICH Q6B) + Impurity profiling (ICH Q3A-Q3D). + Stability testing (ICH Q1A).*	*• Dual specifications (API + excipient)* *• Degradation analytics*	*Function-limited specifications (size, surface charge, etc.)*
Approval Process	*NDA/BLA (New Drug Application (NDA) or Biologics License Application (BLA)*	*• Request for Designation (RFD) to FDA's Office of Combination Products (OCP).* *• Hybrid dossier (MAA)*	*DMF/IID listing (Drug Master File / Inactive Ingredient Database)*
Guidance Documents	*- ICH M4Q (Common technical document, CTD format).* *- ICH S6(R1) (Preclinical safety).* *- FDA's "Draft Guidance on Nanotechnology" (2022).*	*• 21 CFR Part 3 (Primary Mode of Action, PMOA)* *• FDA Theranostics Draft Guidance (2023)*	*ICH Q3C (Residual solvents), Novel Excipient Program; FDA's "Nonclinical Studies for Excipients" (2021).*
Examples	*VivaGel® (SPL7013)[179]*	*• Opaxio™ (paclitaxel-polyglutamate) (NCT00108745)* *• Gadolinium-dendrimer MRI contrasts*	*PEGylated PAMAM in drug delivery.*

6. Future and Outlook

Dendrimer-based nanocarriers have firmly established themselves as promising candidates for CNS delivery, yet their path toward clinical adoption remains complex and multi-faceted. Key areas for the future focus on addressing toxicity, improving BBB permeability predictions, refining biodistribution and targeting, and advancing therapeutic design principles.

6.1. Overcoming Toxicity Challenges

While strategies such as PEGylation, acetylation, and zwitterionic modifications have greatly improved dendrimer biocompatibility, future efforts must extend beyond surface masking. The emergence of "stealth" dendrimers, featuring biomimetic coatings such as CD47-mimetic peptides, and biodegradable backbones [180, 181], reflects a paradigm shift toward intrinsically safer and biologically adaptable materials. Comprehensive toxicity mitigation strategies (see Table 4) will be essential, especially as we move toward chronic CNS indications requiring repeated administration.

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Table 4: Strategies for mitigating dendrimer toxicity: Mechanisms, experimental evidence, and efficacy of surface modifications, complexation approaches, and structural designs

Strategy	**Mechanism of Action**	**Key Experimental Evidence**	**Toxicity Reduction Achieved**
PEGylation	Poly(ethylene) glycol chains shield cationic surface charges, reducing electrostatic interactions with biological membranes	• G5 PAMAM: 12-fold increase in IC50 compared to native dendrimer [133] • G3/G4 DAB dendrimers: 3.4-fold decrease in cytotoxicity in B16F10-Luc cells [134]	Hemolysis reduced from 80% to 12%
Acetylation	Neutralization of surface amine groups minimizes membrane disruption and cytokine activation	• G4 PAMAM: >90% cell viability maintained in MCF-7 and A549 cells at >80% acetylation [136] • Complete elimination of LDH leakage at concentrations up to 20 µM [137]	Cellular toxicity reduced by 10-fold
Carbohydrate Conjugation	Hydrophilic sugar moieties enhance solubility and reduce non-specific cellular binding	• Lactose-functionalized G2 dendrimers: No significant toxicity observed up to 390 µM in A549, DU-145, and HT-1080 cells [138] • Galactose-PPI: Hematotoxicity reduced from 49.2% to 7.1% in G5 dendrimers [139]	Systemic exposure toxicity minimized
Lipid Encapsulation	Liposomal coatings physically shield cationic dendrimer surfaces (Dendrosomes)	• Dendrosomes (Dipalmitoylphosphatidylcholine: Cholesterol, DPPC:CH 85:15): No renal toxicity observed versus uncoated dendriplexes [141] • Complete prevention of ALT/AST elevation in bloodstream [140]	Organ-specific toxicity eliminated
Polyelectrolyte Complexation	Anionic polymers (heparin, DNA) neutralize cationic charges via electrostatic interactions	• Heparin-conjugated PAMAM (P-SS-Hep): Eliminated cytotoxicity while maintaining drug solubility [142]	Inflammatory response significantly reduced
Biodegradable Backbones	Ester bond incorporation enables enzymatic degradation and metabolic clearance	• G3 polyester dendrimers: No hepatic fibrosis observed after 4 weeks versus non-degradable PAMAM [143,144] • Maintained antibacterial activity without cytotoxicity in human fibroblasts	Long-term accumulation prevented
Zwitterionic Modification	Balanced cationic/anionic surface groups prevent membrane disruption while maintaining stability	• Zwitterionic coating: Improved fibroblast viability from 4% to 80% at 0.5 mg/mL [145] • Sulfobetaine conjugation: no cytotoxicity observed [146]	Hemolytic potential abolished
Anionic Surface Groups	Carboxyl or hydroxyl termination reduces cellular adhesion and immune recognition	• G3.5 PAMAM-COOH: Significantly reduced hemolysis versus NH_2-terminated counterparts [147] • Demonstrated safety in zebrafish models at 100 mg/kg [148]	Immunogenicity minimized
Targeted Ligand Conjugation	Receptor-specific moieties (folate, galactose) enhance tissue specificity	• Galactose-PPI: Improved hepatic targeting with 70% reduction in hematotoxicity [139] • Folate conjugation: Reduced systemic immunogenicity while maintaining therapeutic efficacy [149]	Off-target effects substantially reduced

6.2. Leveraging AI for BBB Permeability Prediction

The integration of artificial intelligence (AI) and machine learning (ML) is poised to transform dendrimer design by predicting BBB permeability and optimizing particle characteristics for safety and efficacy (Box 3). This approach can accelerate the rational design of next-generation dendrimers with

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improved CNS delivery profiles and minimized off-target effects [182, 183]. The predictive power of AI/ML tools is only as strong as the data used to train them. To improve the relevance of BBB models for dendrimers and nanocarriers, community-wide data sharing is essential: reporting and standardizing the physicochemical and biological properties of nanocarriers used, as well as BBB permeability results from *in vitro* and *in vivo* studies. This should also include negative results and unpublished data which are often overlooked.

Recent work demonstrates how ML can quantitatively predict BBB permeation of polymeric nanoparticles by integrating physicochemical and biological descriptors into supervised learning models [184]. The dataset, compiled from 112 peer-reviewed articles, included 206 unique nanoparticle formulations, which were divided into 70% training and 30% testing sets for model development and validation. Defining input parameters was challenging, however, were divided into: hydrodynamic diameter, polydispersity index, zeta potentials, core composition (PLGA, chitosan, PEG-PLA, poloxamer, albumin), surface chemistry (PEGylated, ligands functionalized like transferrin, lactoferrin, or antibodies, or unmodified), drug loading capacity, encapsulation efficiency, in vitro BBB model used (hCMEC/D3 human endothelial cells or bEnd.3 murine endothelial cells), transendothelial electrical resistance (TEER), and, in vivo parameters (model species, administration route, dosing levels and circulation times). The output variable was typically quantitative brain uptake (percentage of injected dose per gram of brain tissue or brain-to-plasma ratio for in vivo studies), and apparent permeability coefficients (Papp) for in vitro assays. Among the tested algorithms, random forests achieved the best predictive performance (R^2=0.84; RMSE=0.062) on the test set, outperforming support vector machines and multiple linear regression. This improvement was largely due to the model's ability to capture non-linear relationships, for example the interplay between particle size, surface charge, and ligand density in determining BBB penetration efficiency.

While this approach offers a useful methodological starting point, it cannot be directly applied to dendrimers because the current dataset lacks dendrimer-specific structural descriptors. For dendrimers, important features include generation number, branching density, internal cavity volume, multivalent surface functionality, conformational flexibility under physiological conditions, and whether the payload is covalently attached or encapsulated. Unlike self-assembled polymeric nanoparticles, dendrimers are monodisperse macromolecules, so factors such as branch folding and surface group shielding in vivo can strongly affect BBB transport but are absent from existing models. Without large, standardised datasets that capture these features across diseases, species, and experimental setups, models trained on polymeric nanoparticles are unlikely to predict dendrimer

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behaviour accurately. Therefore, applying this framework to dendrimer design will require targeted data collection, harmonised reporting, and explicit inclusion of dendrimer-specific descriptors in future machine learning models.

6.3. Advanced Systems

The quest for precision CNS delivery has driven remarkable innovations in nanocarrier design, many of which hold significant promise for adaptation to dendrimer platforms. While conventional ligand functionalization has improved dendrimer brain uptake, emerging approaches from broader nanomedicine research demonstrate principles that could revolutionize dendrimer-based delivery systems.

Biomimetic coating strategies, originally developed for polymeric nanoparticles, may be effectively adapted for dendrimer-based therapeutics. Hybrid membranes derived from MDA-MB-231Br brain-tropic cancer cells and erythrocytes were used to functionalize nanoparticles, enabling selective binding and penetration across the inflamed BBB through tumor specific recognition motifs [185]. This approach led to enhanced delivery of dexamethasone and embelin, which inhibited the secretion of neuroserpin and serpin B2, restored local plasmin activity, resulting in suppression of metastatic tumor growth. Given dendrimers' well-defined surface architecture and high degree of functionalization, similar membrane protein coating strategies could be applied to engineer dendrimer platforms with BBB-targeting and immune-evasive properties. These could enable precise delivery of serpin inhibitors and support dendrimer-based combination therapies for treating brain metastases [185].

Similarly, protein-based biomimetic cores highlight design principles transferable to dendrimers. Recently, Huang et al. developed self-assembling therapeutic proteins with hyaluronic acid (HA) and protamine (PRTM) to form a core mimicking the natural cell matrix, encapsulating this core within ApoE3-reconstituted high-density lipoprotein (rHDL) for targeted delivery and enhanced BBB penetration. This platform successfully delivered catalase (CAT) into the CNS of TBI and ALS mouse models, resulting in significant improvements in cognitive and motor functions, reduction of disease progression markers, and extended survival [186].

Aptamer technology has shown promise for CNS targeting [187]. Aptamers are synthetic oligonucleotides that are selected through an iterative process (Systematic Evolution of Ligands by Exponential Enrichment – SELEX) to bind targets with high affinity. As compared to antibodies, aptamers are smaller, easier to chemically modify to increase physiological stability or enable surface

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conjugation, thermally more stable and less immunogenic. Several SELEX methodologies have identified brain penetrating aptamers, in vitro [187] or in vivo [188]. Zhao et al. developed a TfR-targeted aptamer-drug conjugate (ApDC), HG1-9-MMAE, which crosses the BBB by targeting highly expressed TfR on brain endothelial and glioblastoma cells. It demonstrated potent antitumor activity in vitro (bEnd.3 and U-87 MG cells) and in vivo, reducing tumor volume and improving survival [189]. Other aptamers are being explored for targeting glioblastoma stem cells (GSCs), a subpopulation resistant to standard radiotherapy and chemotherapy and implicated in tumor recurrence. Using differential cell SELEX, two RNA aptamers 40L and its truncated form A40s were identified as selective for stem-like GBM cells, binding the ephrin type-A receptor 2 (EphA2) and rapidly internalizing into target cells. Both aptamers inhibited GSC growth, stemness, and migration. A40s was able to cross the BBB after intracardiac injection in mice and remained stable in human serum for up to seven days in vitro, as confirmed by gel electrophoresis and qRT-PCR quantification in brain hemispheres [190]. Interestingly, dual-targeted nanocarriers are easily accessible with aptamer technology thanks to their tunable chemistry. In one study, transferrin (TF) and AS1411 aptamer were co-conjugated onto docetaxel (DTX) and gadolinium (Gd) loaded micelles to enhance both therapeutic efficacy and MRI-based imaging in brain cancer. These micelles exhibited a favorable size range (117–170 nm), high DTX encapsulation efficiency (up to 92.6%), and sustained biphasic drug release over 72 h. Dual-targeting (GDTP–TF–AS1411) significantly reduced the IC50 in glioma cells (0.19 μg/mL) compared to Taxotere® (2.73 μg/mL) and achieved higher brain accumulation in vivo, as indicated by increased AUC values (1.8x) [191]. Such technologies can be integrated with dendrimers as dendrimers' surface functional groups allow for controlled aptamer conjugation while maintaining targeting specificity. The modular nature of both technologies enables creation of "mix-and-match" systems where different aptamers could be conjugated to optimize delivery for specific diseases.

Viral-inspired transduction peptides offer another targeting avenue adaptable to dendrimers. For instance, PepH3, a cationic peptide from Dengue virus type-2 capsid protein, facilitates BBB transcytosis and intracellular delivery. When conjugated to nanoparticles carrying single-domain antibodies (sdAbs) targeting Aβ oligomers, these NPs showed enhanced uptake into brain endothelial cells and transcytosis across rat and human BBB models [192]. This technology could be adapted to dendrimers as well.

To realize the full potential of dendrimer nanotherapeutics for CNS diseases, future efforts must prioritize a comprehensive mapping of BBB alterations across disease contexts. It is also important to

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focus on the creation of scalable, reproducible synthesis methods with advanced characterization tools, as well as the establishment of clear regulatory pathways tailored for nanotherapeutics. Ultimately, interdisciplinary collaboration between chemists, clinicians, and regulatory experts will be essential to harmonize innovative design with clinical translation, ensuring dendrimers achieve their full potential as multifunctional nanotherapeutics for CNS diseases.

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Box 3: AI-Driven BBB Permeability Prediction Tools

Understanding the Context:

AI and ML offer valuable insights into predicting BBB permeability, but they are not a magic tool. These models do not replace experimental validation; rather, they serve as complementary tools to guide design decisions and prioritize candidates for synthesis and testing. Particularly for complex nanocarriers like dendrimers, AI/ML must be combined with experimental approaches for reliable results. This guide summarizes key AI/ML tools and strategies, with emphasis on how to use them for small molecules and adapting approaches for dendrimers and nanoparticles. Refer to [182] for a detailed overview of these tools.

Table B3.1: Structural Modeling Tools for BBB Permeability Prediction *(Focus on interpreting relationships between molecular structure and BBB permeability.)*

Tool	What It Predicts	Input	Output	Strengths	Limitations
MegaMolBART	*Direct BBB permeability score (logBB, AUC=0.88)*	*SMILES string*	*BBB permeability classification*	*Quick, user-friendly, no manual calculations*	*Primarily for small molecules [193]*
q-RASAR PLS	*logBB values (R^2=0.63–0.69)*	*Molecular descriptors (ring count, bond types)*	*Numerical logBB prediction*	*Interpretable, highlights key molecular features*	*Accuracy moderate, manual descriptor preparation needed [194]*
MD Simulations (Molecular dynamics)	*logBB with high precision (R^2=0.90–0.94)*	*3D molecular structure*	*Predicted logBB*	*Physicochemically grounded, high accuracy*	*Computationally intensive, time-consuming [195]*

Key Concepts:

- ***logBB****: Brain-to-blood concentration ratio. Values >0.3 suggest effective BBB crossing [196].*
- ***logP****: Lipophilicity expressed as octanol-to-water concentration ratio; optimal for BBB is 1–3 [195].*

- ***AUC (Area Under Curve):*** *Measures model performance for binary classification (e.g., yes/no BBB permeability). Ranges from 0.5 (random guessing) to 1.0 (perfect prediction). Higher AUC means better model discrimination between BBB-permeable and non-permeable molecules [197].*

Table B3.2: Machine Learning Classifiers for BBB Permeability *(Leverage large datasets to predict BBB permeability without explicitly modeling physical interactions).*

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Model	*Input*	*Output*	*Key Metrics*	*Access & Use*
DeePred-BBB	*1917 molecular features*	*"BBB+" or "BBB-"*	*AUC=0.98, Accuracy=98.07%*	*Free, GitHub repository [198]*
LightBBB	*Molecular descriptors 2432 1D/2D generated using Dragon Software (molecular weight, atoms, etc)*	*Probability score for permeability*	*AUC=0.93*	*High interpretability, scalable[199]*
Linear mixed-effect models	*Nanoparticle size, charge, surface properties (e.g., PEGylation),etc.*	*Custom permeability score*	*R^2= 0.767*	*GitHub repository present [200]*

Best Practices:

- *For Quick Screening of Small Molecules: Use MegaMolBART or DeePred-BBB for rapid yes/no decisions.*
- *For Detailed logBB Predictions: Opt for MD simulations when molecular structures are well-defined.*
- *For Dendrimers & Nanoparticles: Start with small-molecule predictions, then adjust inputs (e.g., add surface chemistry, flexibility) in linear mixed-effect models. Validation with in vitro BBB models is essential.*
- *For Open Access & Experimentation: DeePred-BBB is an excellent starting point for quick in silico permeability assessments.*

Conflicts of interest

The authors declare no conflict of interest.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Acknowledgements

This work was supported by a grant overseen by the Fonds de Recherche du Québec – PBEEE / Bourses de doctorat en recherche Québec-Inde (FRQ-NT, demande # 353411; https://doi.org/10.69777/353411), Fonds de Recherche du Québec Santé (FRQ-S, demande # 348525; https://doi.org/10.69777/348525) and Natural Sciences and Engineering Research Council of Canada (NSERC grant #RGPIN-2018-06636). During the preparation of this work, the authors used ChatGPT version 4.0 to improve language and readability

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of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Author contribution

Conceptualization: P.B., V.G.R, J.L.C; Visualization: P.B.; Writing – original draft: P.B.; Writing – review and editing: P.B., V. G.R., J.L.C.; Funding acquisition: V.G.R.; Supervision: V.G.R, J.L.C.

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View Article Online
DOI: 10.1039/D5NR02548F

Crossing the Blood-Brain Barrier: Advances in Dendrimer-Based Nanocarriers for Central Nervous System Delivery

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Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.