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REVIEW

Brain Targeting Nanomedicines: Pitfalls and Promise

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Abstract: Brain diseases are the most devastating problem among the world's increasingly aging population, and the number of patients with neurological diseases is expected to increase in the future. Although methods for delivering drugs to the brain have advanced significantly, none of these approaches provide satisfactory results for the treatment of brain diseases. This remains a challenge due to the unique anatomy and physiology of the brain, including tight regulation and limited access of substances across the blood-brain barrier. Nanoparticles are considered an ideal drug delivery system to hard-to-reach organs such as the brain. The development of new drugs and new nanomaterial-based brain treatments has opened various opportunities for scientists to develop brain-specific delivery systems that could improve treatment outcomes for patients with brain disorders such as Alzheimer's disease, Parkinson's disease, stroke and brain tumors. In this review, we discuss noteworthy literature that examines recent developments in brain-targeted nanomedicines used in the treatment of neurological diseases.

Keywords: brain delivery, blood-brain barrier, targeted delivery, nanoparticle, neurodegenerative diseases, stroke, cancer

Introduction

In 1885, Paul Ehrlich made a groundbreaking discovery: intravenous injection of dyes stained all organs except the brain.[1] This discovery illuminated the existence of the highly restrictive biological barrier in the central nervous system (CNS) known as the blood-brain barrier (BBB).[2] The BBB is essential for protecting the CNS from toxins, drugs, and pathogens. Most of the BBB surface consists of thin capillaries in which tight BBB connections occur between endothelial cells, preventing chemicals from entering the brain paracellularly.[3] In addition to endothelial cells, brain cells such as pericytes and astrocytes build and maintain the BBB. The BBB can only be penetrated passively by lipid-soluble solutes that can readily diffuse across the capillary endothelial membrane.[4] As a result, about 98% of small molecules, virtually all large molecules and most biological drugs are excluded from the BBB.[5] The integrity of the BBB is critical for the proper functioning of the CNS. Conversely, disruption of the BBB is a key element in the development of many brain disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), stroke and several others.[6–9]

As the world population ages, the global burden associated with neurological disorders increases worldwide, accounting for more than 6% of all diseases[10] and costing more than US$1.7 trillion annually in the US and Europe alone.[11,12] In recent years, CNS diseases have become a leading cause of disability-adjusted life years and one of the most common causes of death and disability in the world.[13] Over the past 30 years, neurological diseases have increased disability-adjusted life years and mortality by 15% and 39%, respectively.[14] The number of people with dementia is estimated to increase from ~57 million cases worldwide in 2019 to 152 million cases in 2050.[15] AD, PD, stroke, multiple sclerosis and amyotrophic lateral sclerosis (ALS) are just some of the incurable CNS diseases. Most available medications only relieve symptoms and do not affect the progression of the disease.

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Thus, there is an urgent need for more effective drug delivery methods and disease-modifying drugs that can slow down or stop neurodegeneration and cure neurological disorders. The goal is to stop neurodegeneration and regenerate still alive neurons.

Drug delivery to the CNS remains a major therapeutic challenge. Delivery of therapeutics across the BBB is considered a minimally invasive strategy to target the brain. However, most preclinical and clinical studies to date show the relative lack of success that researchers in this field have achieved. Notably, only 3–5% of brain-directed pharmaceuticals have reached the market in recent years.[16] The greatest challenges in development of systemically-administered CNS drugs include low brain delivery due to insignificant BBB permeability,[17] increased BBB disruption due to the drug's pathway of entry into the brain,[18,19] and systemic toxicity due to poor drug selectivity. To overcome these challenges, several administration routes have been explored including intranasal and intracranial routes.[20–22] Focusing on intravenous administration, nanosized carriers (nanoparticles (NPs), size >100 nm)[23] are increasingly being developed for more efficient drug delivery across the BBB for the treatment and diagnosis of a wide range of CNS diseases, such as cancer and neurodegenerative diseases.[5,24–26] In addition, different precision targeting strategies (eg, functionalization with antibodies, ligand proteins or homing peptides) have been explored to facilitate drug uptake into the brain.[27,28] This review summarizes noteworthy literature examining recent advances in brain drug delivery using nanomaterials for the treatment of neurological diseases.

Current Approaches and Challenges in Brain Drug Delivery

In recent years, the challenges of drug delivery in brain diseases have been increasingly recognized and studied. Despite this rapid progress, barriers to drug delivery often vary by disease and delivery method. The delivery of the drug into the CNS through the cardiovascular system is prevented by physiological and physical obstacles, including the BBB at the level of the cerebrovascular bed and other specialized barriers, such as the blood-spinal cerebrospinal fluid barrier or the blood-tumor barrier. Consequently, even if a compound reaches the brain, its quantity remains below therapeutically relevant concentrations.[29,30] One reason for this is the drug's design, which limits the compound's ability to reach the brain. The therapeutic agent very often interacts with macromolecules in the body, impairing drug's stability, therapeutic activity, or penetration through the BBB.[31,32] Another problem is the presence of enzymes in the plasma and the CNS tissue that can render the drug inactive.[2,33] For example, brain microvessels have similar to liver metabolic activities due to the presence of enzymes like epoxide hydrolase and uridine 5'-diphospho-glucuronosyltransferase.[33] In this section, we discuss the architecture of the BBB, as well as brain drug delivery strategies and challenges.

Blood-Brain Barrier (BBB)

The neurovascular interfaces in the brain, spinal cord, retina, and peripheral nerves are essential to maintain the health and functionality of these delicate tissues.[34,35] These interfaces are safeguarded by specialized blood-tissue barriers that exclude harmful substances and immune cells while allowing necessary molecules and nutrients to pass through. The BBB is a highly restrictive barrier that is essential for normal hemostasis and optimal functioning of the CNS. Complex cellular and noncellular components work together to keep the BBB functioning. Low permeability of the BBB is controlled by complex crosstalk between brain microvascular endothelial cells (BMEC), pericytes, astrocytes (Figure 1A) with other cell types in the brain parenchyma (eg, microglia, neurons, oligodendrocytes).[36] The transmembrane proteins in structures connecting endothelial cells known as tight junctions form a highly selective network that forces the majority of molecular traffic toward a transcellular route (ie, through cells), rather than the paracellular route (ie, between cells).[36] Tight junctions are composed of a complex of ~40 different proteins including transmembrane cell adhesion proteins such as claudins, occludins, and junction adhesion molecules.[37] Pericytes surrounding the BMEC are in close contact with the endothelial cells and communicate with them through gap and adherens junctions.[38–40] Astrocytes are star-shaped cells of ectodermal origin, have processes known as perivascular endfeet that are applied to the walls of microvessels.[41] Whereas the astrocytic endfoot cover of the blood vessel is not considered to be a critical element for the physical barrier of the BBB,[42] these cells are essential for the formation and maintenance of the BBB by modulating the expression of transporters and receptors and providing factors that contribute to the formation and maintenance of tight junctions between the BMEC.

The BBB exhibits distinct microanatomical and physiological features in different brain regions that are also reflected in differences in the BBB barrier function. For example, due to the higher synaptic and metabolic activity of neurons, grey matter has a higher capillary density than white matter.[43] In addition, the morphology of astrocytes differs in grey and white matter.

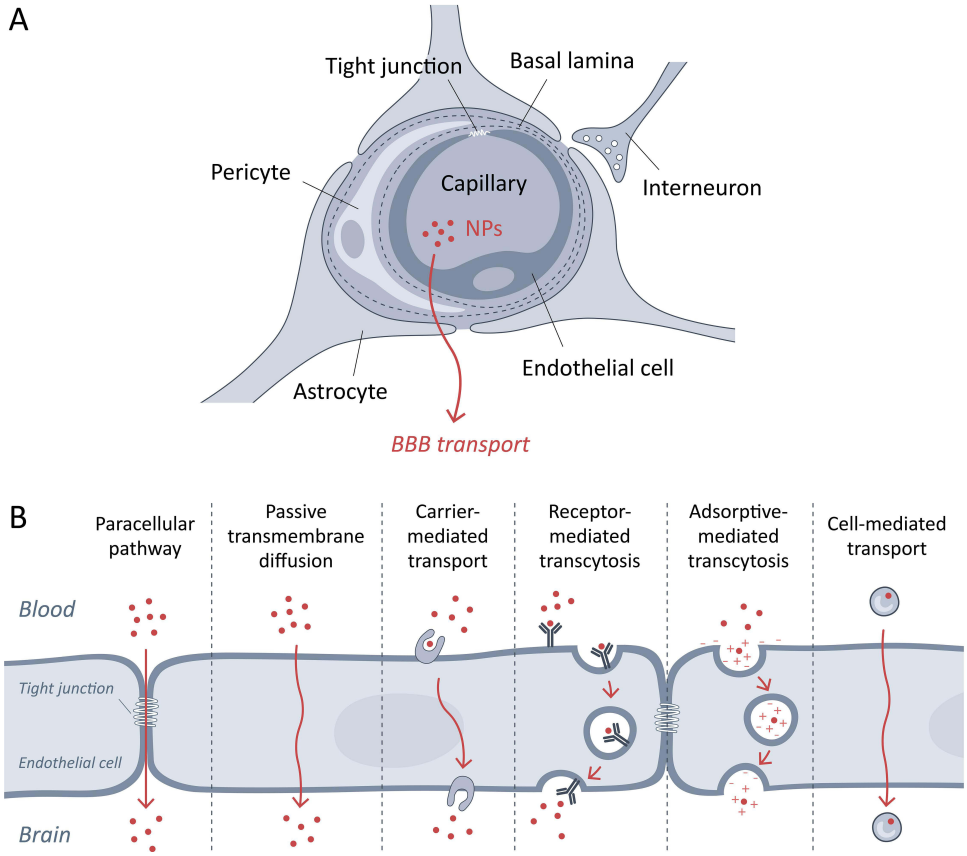

Figure 1 Schematic structure of the blood-brain barrier (BBB) (**A**) and transport mechanisms of nanoparticles (NPs) through the BBB (**B**). NPs can cross the BBB by paracellular pathway, passive transcellular diffusion, carrier-mediated transport, receptor-mediated transcytosis, adsorptive-mediated transcytosis, and cell-mediated transport.

Specifically, the most common type of astrocytes in grey matter is protoplasmic, whereas the majority of astrocytes in white matter are fibrous.[44] Regional differences are also observed in pericytes. For example, the highest pericyte coverage is present in the cortex, hippocampus and caudate nucleus, whereas the cervical, thoracic and lumbar spinal cord anterior horn capillaries have lower pericyte coverage and show higher permeability than the brain microvessels.[45] High diversity of glial sub-populations throughout the CNS was also seen using single-cell transcriptomics.[46] Furthermore, the cerebral endothelial cell gene expression diverges across the vascular tree (arterioles, capillaries, and venules). Notably, solute transport-related genes such as monocarboxylate transporter 1 and plasma membrane Ca^{2+} ATPase Type 2 exhibit higher expression in capillaries compared to venules.[47] Cerebral and pial microvessels in the brain also display differences, with pial microvessels lacking astrocytic end feet showing lower barrier function.[48]

Molecular Transport Across the BBB

The brain cannot synthesize most of its required nutrients and thus relies on supplies from the circulation system. Due to the presence of tight junctions between the endothelial cells of the capillaries, which almost completely exclude the possibility of paracellular transport, most of the molecules essential for the brain cross the BBB through a transcellular route. Small lipophilic molecules with a mass of less than 500 Da can in most cases cross the BBB by simple diffusion.[49] Most nutrients, however, do not meet size criteria for passive diffusion and rely on membrane transporters or carriers to extravasate and enter the brain.[36,50] These transporters are either concentration-dependent (facilitated diffusion transporters) or energy-dependent (active transporters). The transporter-mediated uptake is typically ~10 times faster than transmembrane diffusion, saturable, and structure-specific. Larger macromolecules cannot follow this pathway and use receptor-mediated transport to pass into and out of the brain. Various receptors on the surface of BMEC bind specific ligands and trigger the uptake of the compounds into a vesicle, with subsequent receptor-mediated uptake and different traffic routes including lysosomal degradation, recycling back to the apical membrane or

routing to the basolateral membrane where membrane fusion allows for the release of the vesicle content (transcytosis). The type of receptor and intravesicular environment determine whether endocytosis or transcytosis occurs.[51] The heterogeneous distribution of receptors throughout the BBB allows for the transportation of the macromolecules to specific areas of the brain. In addition to physical BBB alteration techniques (eg, using osmotic agents, electromagnetic fields, or microbubbles that oscillate in response to the application of ultrasound, leading to transient opening of the BBB),[52,53] the aforementioned transcellular pathways are used to deliver therapeutics into the brain parenchyma.

Strategies to Cross the BBB and Drug Delivery Challenges

Strategic therapeutic approaches for drug delivery to the brain can be divided into two broad categories: BBB bypass and BBB crossing. Perhaps one of the least invasive methods of bypassing the BBB is the intrathecal injection of therapeutic agents into the subarachnoid space of the spinal cord.[18] Although the cerebrospinal fluid flows in opposite direction to desired drug delivery, this administration method has been shown to successfully deliver therapeutics to the brain tissue.[54] To bypass the BBB, intracerebral administration can also be used, allowing release of the drug into the brain parenchyma through an implant or injection.[55] This route can be used for brain delivery of a wide range of compounds and formulations. Although intracerebral administration has some advantages, such as reduced systemic toxicity, its significant disadvantages include poor drug diffusion, and the invasive and risky nature of the procedure that can cause infections. In addition, this method is expensive, requires complicated brain surgery and hospitalization. Intranasal administration is another method of bypassing the BBB. This method is non-invasive and does not require injections, however, clinical observations over the past 40 years have shown inconsistent results.[56]

In the context of trans-BBB delivery, drugs can enter the CNS via the paracellular pathway, passive transcellular diffusion, carrier-mediated transport, receptor-mediated transcytosis, adsorptive-mediated transcytosis, or cell-mediated transport (Figure 1B). Although, intracellular pores are normally only around 1 nm, in various brain pathologies or as a response to certain physicochemical stimuli, the BBB confluency may be disrupted, increasing drug extravasation and penetration into the brain.[6,8,57] As disused above, passive transcellular diffusion is only available for small (below 500 Da) lipophilic molecules. Transporters that are involved in carrier-mediated transport are structure-specific and rarely transport drug analogues. As such, drug molecules must be chemically modified to mimic the normal ligands. Receptor-mediated transcytosis relies on BBB-expressed proteins/receptors to transport therapeutics from the blood to the brain. This delivery strategy may be applied to different targeting ligands such as antibodies, proteins, peptides, and aptamers. Being a non-invasive method, it can be used for repeated drug delivery. Receptor-mediated transcytosis is widely used for the delivery of the NPs across the BBB,[58] and its application in targeted drug delivery is discussed in more detail below. Cell-mediated transport differs from previously discussed pathways and relies on the internalization of the therapeutic agent by immune cells such as monocytes or macrophages and subsequent transport across the BBB into the brain.[59,60]

Targeted Drug Delivery

Improvement of physicochemical or biological properties of drugs is usually achieved by structural alterations of the molecule or, in the case of nanomaterials, modifying the surface of the particle. The purpose of such functionalization can be improved pharmacokinetics (eg, longer half-life and prolonged systemic circulation), better penetration through biological barriers (eg, the BBB) or specific organ/tissue targeting (eg, brain or tumor). To extend the blood circulation half-life of the NP, one of the oldest practices is particle functionalization by polyethylene glycol (PEG).[61] Furthermore, noncovalent functionalization of the particle surface with surfactants such as polysorbate 80 (Tween 80) or poloxamer 188 has been shown to guide NPs to the brain via adsorption of apolipoproteins,[62] facilitating interaction with BMEC and transport of NPs across the BBB.[30,63,64] By counteracting the nonspecific adhesion due to van der Waals interactions, PEGylation opens the opportunity for targeting of NPs with targeting moieties such as antibodies and homing peptides.[65,66] These ligands either engage with the endocytosis or transcytosis receptors expressed on the BMEC surface (eg, transferrin, insulin, lactoferrin, and lipoprotein receptors), penetrate directly through cellular membranes (cell-penetrating peptides (CPP)),[65,67,68] or used mixed pathways for BBB penetration. NP-CPP conjugates were the first BBB-crossing NPs that did not compromise the integrity of the BBB.[69,70] CPP are typically endocytosed, with the conjugated therapeutic agents becoming captured inside endosomes.[71,72] Endosomal escape is not fully understood,[73,74] and represents a major barrier to the usage of CPP as delivery systems. Strategies to facilitate endosomal escape have been described in a recent review by Ghorai et al.[27] Another significant drawback of CPP, lack of cellular selectivity, can be enhanced by the inclusion of

receptor-specific modules to target specific organs, tissues or cells.[75] Brain-targeting peptides can enhance drug or NP interactions with BMEC, increase uptake, and consequently transport therapeutic payloads across the BBB, delivering drug molecules to the brain.[28,76–78] BBB targeting peptides are derived from various sources, such as viral proteins (human immunodeficiency virus (HIV) (HIV-1-TAT),[79] rabies virus,[80]), phage biopanning screens (Pep-22, TGN, G23, T7, THR),[81] venom neurotoxins (Apanin, MiniAp),[82] and different endogenous proteins (regulon polypeptides, receptor-associated protein, Kunitz protease inhibitor domains).

Nano-Based Approaches Towards Drug Delivery to the Brain

Nanoparticles have been demonstrated to translocate across the BBB either by carrier-mediated transcytosis, adaptive-mediated transcytosis, or receptor-mediated transcytosis (Figure 1B). The ability of the nanoformulated drug to cross the BBB is determined by the physicochemical and biological properties of the NPs, and not by the chemical structure of the drug. The biodistribution of NPs is significantly influenced by their physicochemical characteristics, including particle size, shape, charge, and surface modifications. To improve NP transport across the BBB and enhance cellular uptake, NPs are often decorated with molecules, polymers, or targeting ligands such as small compounds, antibodies or homing peptides.[82,83] For example, NPs coated with transferrin, apolipoproteins,[64] and insulin-like growth factor II[84] have been shown to be more effective at penetrating the BBB than nonfunctionalized NPs.[85] Nanomedicine approaches to treat brain diseases are discussed in more detail below.

Application of Nanomaterials for Neurodegenerative Disease Therapy

AD, PD, ALS, and Huntington's disease (HD) are among the most common and harmful brain disorders. The mechanisms of onset and progression of neurodegenerative diseases still remain an unresolved issue, and disease-modifying treatments are currently lacking.[86,87] Immune activation within the CNS and neuroinflammation is associated with neurodegenerative diseases.[88] In addition, oxidative stress and endoplasmic reticulum stress induced by aggregated proteins are the most common denominators of neuronal cell loss.[89,90] Some genetic risk factors can also contribute to the development and progression of neurodegenerative diseases. For example, Familial Alzheimer's disease is caused by inherited mutations in presenilin 1 (the most common), presenilin 2 and amyloid precursor protein genes.[91] Familial AD accounts only for 5% of all AD cases but leads to early onset of symptoms.[92] Similarly, mutations in PARKIN, PINK1, FBXO7, PARK7, GBA1 or leucine-rich repeat kinase 2 genes are the most common causes of familial PD.[93] Mutations in alpha-synuclein (αSyn) gene, which encodes αSyn protein, have been found to be linked to familial forms of PD.[94]

Effective treatments for brain diseases are limited due to difficulties in drug delivery. AD, PD, ALS, and HD are complex, multifactorial diseases which have prompted researchers to design multitarget ligands to address the complementary pathways involved in these disorders. In recent years, nanomaterials have found widespread use in several biomedical fields, including neurodegenerative diseases.[29] Pathological misfolding of proteins into amyloid fibrils is a hallmark of several neurodegenerative diseases, including amyloid-beta (Aβ) peptide in AD and αSyn protein in PD. The amyloid hypothesis suggests that an abnormal accumulation of misfolded proteins in the brain causes nerve cell death. In AD, the accumulation of extracellular Aβ in senile plaques and intracellular tau in neurofibrillary tangles over time correlated with memory loss and cognitive decline.[95] Similarly, misfolding and aggregation of αSyn in Lewy bodies, the hallmark of PD, mediate disruption of cellular homeostasis and can cause degradation and death of dopamine neurons in PD.[96,97] Inhibition of amyloid protein aggregation has become one of the popular approaches for the potential treatment of amyloid disease. For example, the US Food and Drug Administration recently approved human monoclonal antibodies aducanumab[98] and lecanemab[99] which target various forms of aggregated Aβ. These antibodies were able to reduce amyloid markers in the early stages of AD but showed modest effect on cognitive functions and were associated with side effects such as brain shrinkage and blood clotting.[100] This suggests that there is still a lot of space for the development of new therapies against AD.[101]

The use of nanotechnology in drug delivery has opened various opportunities to develop better therapeutic agents. For instance, dual functionalization of nanocarriers has been actively explored in past years, demonstrating promising dual-targeting applications. In a recent study, NPs coated with red blood cell membranes and functionalized with a blood-brain barrier-crossing peptide TGNYKALHPHN were used for brain delivery of curcumin, a therapeutic agent for AD.[102] The incorporation of red blood cell membrane coating not only prolonged the circulation half-life of NPs but also resulted in lower immunogenicity compared to nanocarriers relying on synthetic materials. Compared to untargeted nanoformulation, the BBB-targeting resulted in

an ~8-fold increase in curcumin delivery to the brain and resulted in enhanced spatial learning and memory in a mouse model of AD.

PEGylated superparamagnetic iron oxide NPs (SPION) conjugated with Aβ oligomer-specific single-chain variable antibody W20 and class A scavenger receptor activator XD4 (inhibit Aβ aggregation) decreased Aβ aggregation and significantly reversed cognitive deficits as well as ameliorated neuropathology in AD mice (Figure 2A).[103] Furthermore, multifunctional theranostic platform utilizing polymer-coated SPION, coupled with curcumin and decorated with BBB-crossing (CRTIGPSVC) and Aβ targeting (QSHYRHISPAQV) peptides not only successfully traversed the BBB, inducing neuroprotection, but also detected Aβ deposits in vivo through magnetic resonance imaging and reduced plaque burden (Figure 2B).[104] Liu et al synthesized zwitterionic poly(carboxybetaine)-based NPs targeted by mannose analog 4-aminophenyl α-d-mannopyranoside to guide the NPs to penetrate through the BBB and target to microglia, and functionalized by positively charged reactive oxygen species (ROS) responsive polymer poly[(2-acryloyl)ethyl(p-boronic acid benzyl)dimethylammonium bromide].[105] The NPs normalized dysfunctional microglia via two synergistic approaches: 1) fingolimod (immunomodulating medication) and signal transducer and activator of transcription 3 siRNA based inflammatory modulation, and 2) poly(carboxybetaine)-based Aβ microglial recruitment. The synergistic strategy significantly inhibited crosstalk between microglia and Aβ, which attenuated the AD pathology (Figure 2C).

Recently, Lei and colleagues presented an oral brain-targeting delivery system designed for multitarget treatment of AD, coupled with a glucose control strategy (Figure 3A).[106] These PEGylated polymeric NPs effectively traversed the intestinal epithelial barrier and the functionalization with mannose allowed for glucose transporter 1-dependent crossing of the BBB (Figure 3B). In the brain, the released drug load (fingolimod) transformed the microglia's polarization from pro-inflammatory M1 to anti-inflammatory M2, normalized activated astrocytes, contributed to the clearance of toxic Aβ protein, and mitigated oxidative stress and neuroinflammation. In another study, polymeric NPs were dual-targeted with a BBB-penetrating peptide derived from the rabies virus and a neuronal-targeting Tet1 peptide.[107] This nanoformulation demonstrated effective β-site amyloid precursor protein cleaving enzyme-1 (BACE1) or glycogen synthase kinase 3β (GSK3β) siRNA delivery, leading to the suppression of the expression of the Aβ precursor protein cleaving enzyme. This innovative approach significantly ameliorated behavioural deficits in a mouse model of AD. Similarly, nanomedicines based on rabies virus glycoprotein derived peptide and angiopep-2 decorated hydroxide NPs were employed for the delivery of a siRNA and anti-inflammatory drugs. This novel approach successfully inhibited the aggregation of Aβ and mitigated neuroinflammation, contributing synergistically to restore memory and cognitive deficits in AD mice.[108]

Furthermore, Rodrigues et al designed dual-modified liposomes (transferrin and CPP functionalized) for nerve growth factor gene delivery (Figure 3C) and reported successful brain delivery in vivo, cell transfection, and a significant decrease in toxic Aβ species (Figure 3D).[109] Nerve growth factor is important for the treatment of AD because it can reverse atrophy, prevent degeneration, and stimulate the function of cholinergic neurons in the basal forebrain.[111,112] In addition, nerve growth factor levels in the basal forebrain are reduced in patients with AD.[109] Recently, Andrade et al found that caffeic acid-loaded transferrin-functionalized liposomes could prevent Aβ fibrillization and disaggregate mature fibrils.[113] While transferrin has been extensively explored as a brain-targeting ligand for nanomedicines, several factors limit its effectiveness. One prominent issue that limits the capacity of the delivery is the potential saturation of transferrin receptors on the BBB and brain cells. Furthermore, widespread expression of transferrin receptors in different tissues results in accumulation of transferrin receptor targeting ligands in tissues other than brain and triggers potential side effects. Ongoing research aims to refine and optimize transferrin-based strategies, exploring modifications and combinations with other targeting ligands to enhance delivery capacity, specificity, improve transport across the BBB, and mitigate potential immunogenic responses.

Lei et al developed multifunctional self-assembled peptide micelles decorated with ROS scavenger thioketal-glutathione, inhibitor for Aβ aggregation LPFFD, and autophagy activator for degrading Aβ derived from autophagy protein Beclin 1.[110] The resultant nanoformulation showed transport across the BBB, ability to decrease the Aβ plaques and eliminate ROS for AD prevention and treatment. In another study, liposomes were loaded with apolipoprotein E plasmid and functionalized with CPP and glucose transporter 1 targeting ligand mannose to enhance brain-targeting and cellular internalization (apolipoprotein E reduces AD risk, delays the onset of disease, and attenuate the clearance of toxic Aβ proteins from the brain) (Figure 3E).[114] Approximately 2-fold protein expression was observed in the neurons treated with the liposomal formulation. Notably, the inclusion of apolipoprotein E on the outer layer of nanomedicines enhances drug delivery to the brain and uptake by nerve cells. For example, Yu et al developed apolipoprotein E-coated nano micelles delivering Oridonin and Phillyrin to the brains of AD

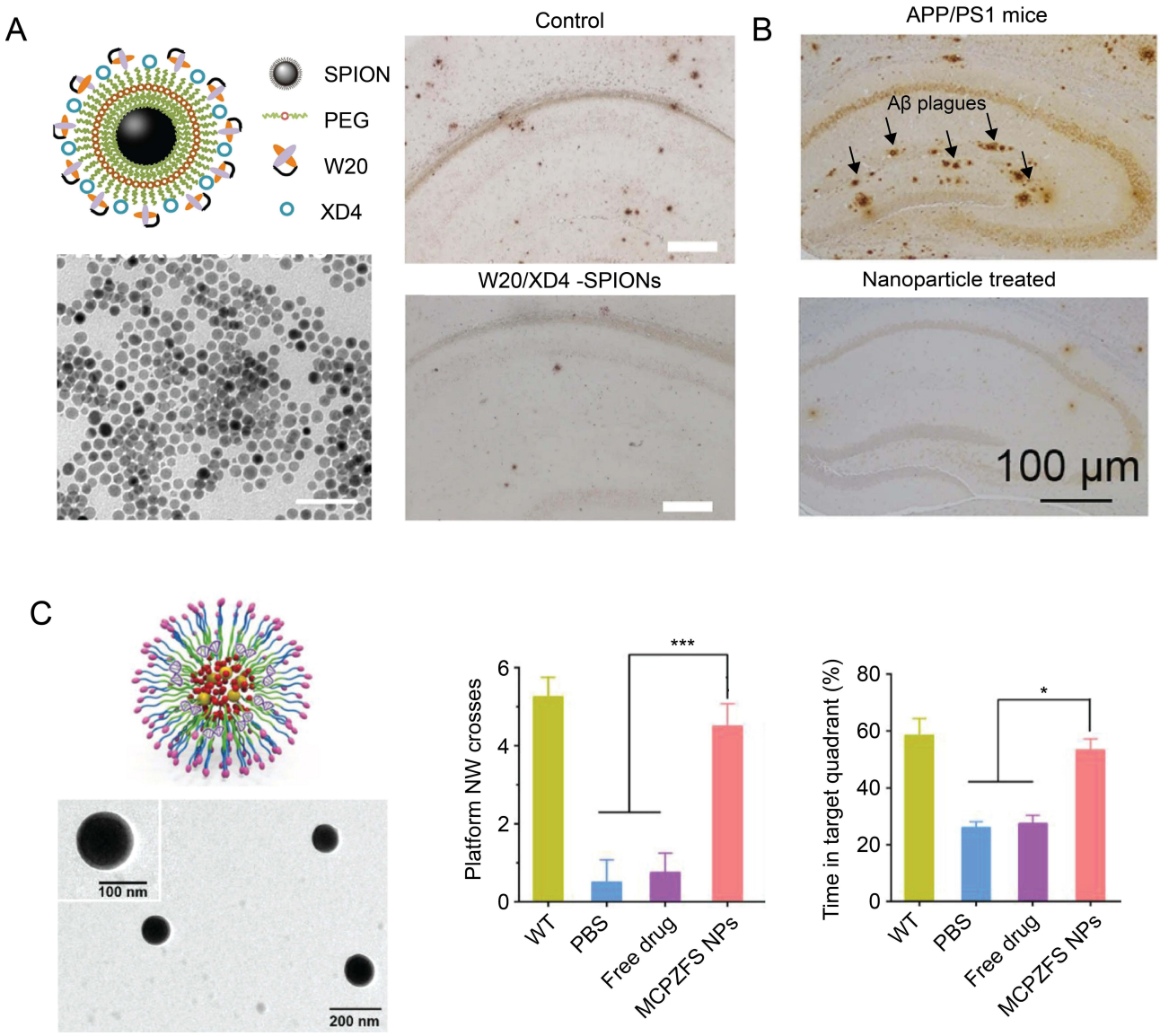

Figure 2 Application of nanomaterials against Alzheimer's diseases. (**A**) W20/XD4-SPION attenuated Aβ pathology in the brains of AD mice. Adapted from Liu X-G, Zhang L, Lu S, et al. Superparamagnetic iron oxide nanoparticles conjugated with Aβ oligomer-specific scFv antibody and class A scavenger receptor activator show therapeutic potentials for Alzheimer's Disease. *J Nanobiotechnology*. 2020;18(1):160. Creative Commons.[103] Schematic illustration and morphology (TEM, scale bar 50 nm) of W20/XD4-SPION (left). 6E10 immunostaining for plaques in the brains of AD mice treated with SPION reduced Aβ burden (right). Scale bars 400 μm. (**B**) Significantly reduced Aβ deposition after treatment by curcumin-loaded and decorated with BBB-crossing (CRTIGPSVC) and Aβ targeting (QSHYRHISPAQV) peptides SPION in double transgenic mice (APP/PS1 mice). Adapted from Ruan Y, Xiong Y, Fang W, et al. Highly sensitive Curcumin-conjugated nanotheranostic platform for detecting amyloid-beta plaques by magnetic resonance imaging and reversing cognitive deficits of Alzheimer's disease via NLRP3-inhibition. *J Nanobiotechnol*. 2022;20(1):322. Creative Commons.[104] (**C**) Schematic illustration and TEM image of the MCPZFS NPs; scale bar: 200 nm (left). MCPZFS NP treatment could significantly attenuate cognitive and memory impairment of AD transgenic mice as demonstrated by Morris water maze test (middle and right). Adapted from Liu R, Yang J, Liu L, et al. An "Amyloid-β Cleaner" for the Treatment of Alzheimer's Disease by Normalizing Microglial Dysfunction. *Adv Sci (Weinh)*. 2019;7(2):1901555. Creative Commons.[105] Data are presented as the mean ± SD. *P < 0.05, ***P < 0.001.

mice, resulting in improved cognitive abilities, alleviated Aβ deposition, and reduced neuroinflammation.[115] Despite being a widely studied brain-targeting ligand, apolipoprotein E poses certain challenges for nanomedicine applications. One key limitation is the polymorphic nature of the apolipoprotein E gene, resulting in different isoforms (ApoE2, ApoE3, ApoE4) with distinct affinities for receptors. This genetic diversity may influence the binding efficiency of apolipoprotein E-conjugated nanocarriers to receptors on the BBB, potentially affecting the ligand's reliability and consistency in brain targeting. Moreover, analogous to transferrin, apolipoprotein E receptors are not exclusive to the BBB; they are expressed in various tissues throughout the body. This non-specific distribution may lead to off-target effects, reducing the selectivity of apolipoprotein E mediated nanomedicines for brain tissues. In overcoming these hurdles, ongoing research seeks to refine apolipoprotein E-based strategies,

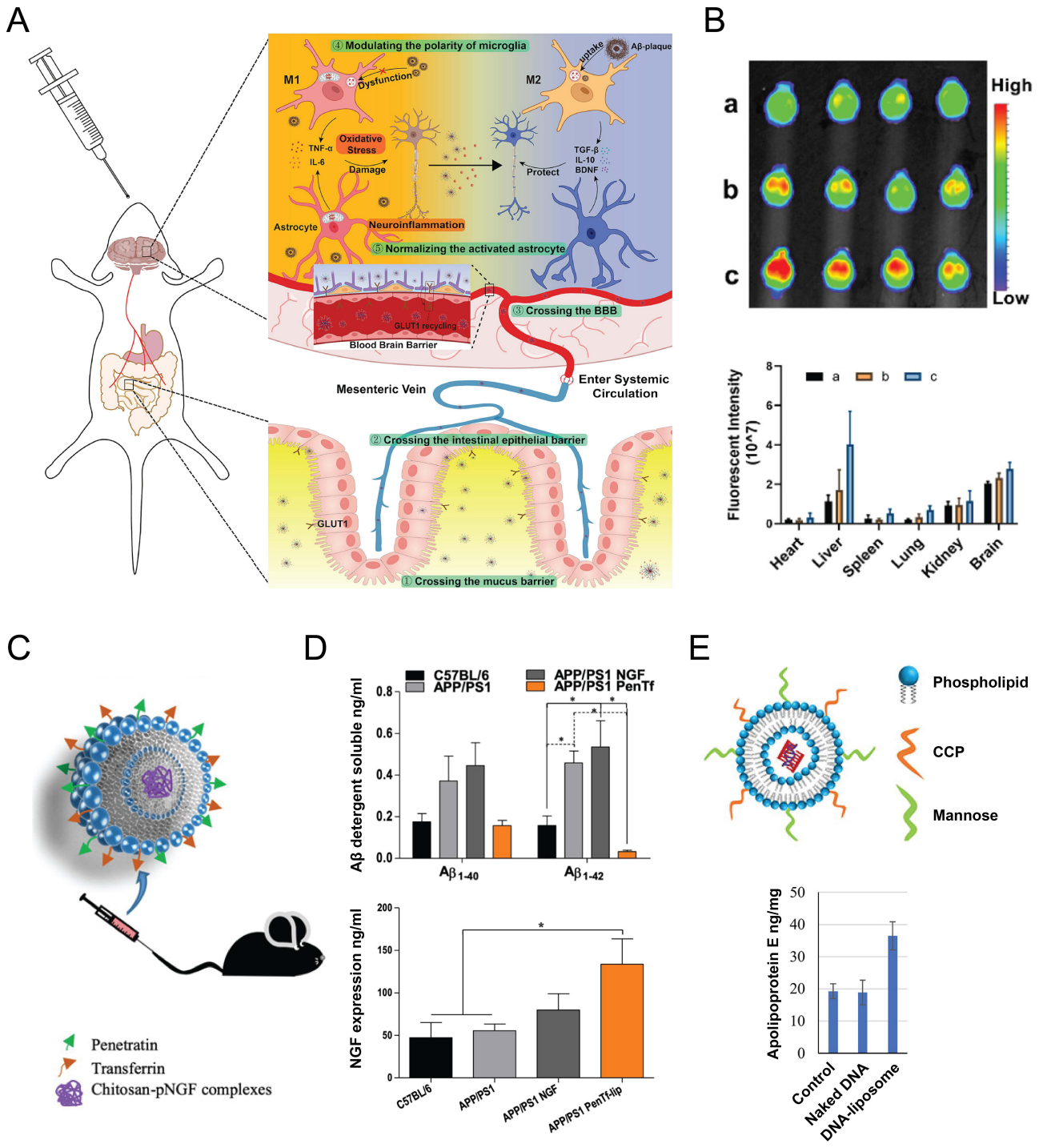

Figure 3 Application of nanomaterials against Alzheimer's diseases. (**A**) Schematic diagram of mannose-guided nanoparticles (NPs) reaching the brain via oral administration and (**B**) organ biodistribution of (a) only PEGylated NPs, (b) mannose functionalized NPs and (c) mannose functionalized in combination with glucose control strategy by administering glucose 1 h after NP administration. Reprinted from Lei T, Yang Z, Jiang C, et al. Mannose-Integrated Nanoparticle Hitchhike Glucose Transporter 1 Recycling to Overcome Various Barriers of Oral Delivery for Alzheimer's Disease Therapy. *ACS Nano*. 2024;18(4):3234–3250. Copyright © 2024 American Chemical Society.[106] By implementing a glucose control strategy, NP accumulation at AD lesions was enhanced, resulting in highly efficient oral brain-targeting. (**C-D**) Delivery of the nerve growth factor (NGF) gene through the blood–brain barrier resulted in a notable reduction in Aβ accumulation in mice with Alzheimer's disease (AD) carrying the APP/PS1 mutation. Liposomes decorated with penetratin and transferrin (PenTf), exhibited effective transfection capabilities. This formulation demonstrated a remarkable capacity to significantly decrease Aβ levels in the brains of APP/PS1 mice. Reprinted from Rodrigues BDS, Kanekiyo T, Singh J. Nerve growth factor gene delivery across the blood–brain barrier to reduce beta amyloid accumulation in AD mice. *Mol Pharm*. 2020;17(6):2054–2063. Copyright © 2020 American Chemical Society.[109] Data are expressed as mean ± SEM (n = 14/group). Statistically significant differences ($p < 0.05$) are shown as (*). (**E**) Liposomes decorated with rabies virus glycoprotein peptide (CCP) and mannose showcased exceptional permeability across the blood-brain barrier (BBB) for gene delivery. Following a single tail vein administration in C57BL/6 mice, these specialized liposomes demonstrated a remarkable twofold increase in Apolipoprotein E expression in the brain. Reprinted from Arora S, Layek B, Singh J. Design and validation of liposomal ApoE2 gene delivery system to evade blood–brain barrier for effective treatment of Alzheimer's disease. *Mol Pharm*. 2021;18(2):714–725. American Chemical Society.[114]

exploring isoform-specific modifications and combination approaches with other ligands to enhance specificity, improve transport efficiency across the BBB, and mitigate potential off-target effects and immunogenic responses.

Several other approaches have been explored in the brain-targeted nanomedicines again neurogenerative diseases. For example, pH-responsive glucose-functionalized polymer nanomicelles enhanced the delivery of anti-Aβ aggregation 3D6 antibody fragments to the brain by up to 41-fold compared with free antibodies.[116] Likewise, Zhou et al used glycosylated siRNA nanoformulations to target BACE1 (β-site amyloid precursor protein cleavage enzyme 1) in amyloid precursor protein/PS1 mice and observed effective delivery of the therapeutics to the brain, ameliorating AD-like pathology.[117]

Nanomedicines have also been developed to target phosphorylated tau and αSyn deposition in PD. In a recent study, phosphatidylserine liposomes encapsulated with astragaloside IV (decrease αSyn expression) and nesfatin-1 (anti-apoptotic characteristics by suppressing rotenone-induced αSyn aggregation), and grafted with wheat germ agglutinin (BBB transport via receptor-mediated endocytosis) and leptin (BBB transport by either direct penetration or transcytosis via interaction with leptin receptor) demonstrated excellent BBB permeability, protection of dopamine neurons from apoptosis, reduced expression of αSyn and phosphorylated tau in vivo.[118] Gao et al applied surface-modified MgO NPs for targeted treatment of PD.[119] The NPs were coated with polydopamine and plasmid DNA, and functionalized by PEG, lactoferrin (to improve solubility and target the BBB) and puerarin (to inhibit oxidative stress and cell apoptosis). This multi-targeting nanomedicine inhibited cell apoptosis by suppressing the expression of αSyn and reducing ROS levels. In addition, NPs showed neuroprotection and recovery of the motor functions in (1-methyl-4-phenyl-1,2,3,6- tetra hydropyridine induced PD mouse model. Liposomes decorated with transferrin were employed for the targeted delivery of an anti-αSyn antibody to the brain.[120] These brain-targeted liposomes achieved a sevenfold increase in antibody concentration within brain cells, leading to reduced αSyn aggregation, alleviated neuroinflammation, and improved behavioural motor function and learning ability in mice. Similarly, liposomes modified with transferrin and rabies virus glycoprotein demonstrated improved BBB-targeting and delivery of epigallocatechin gallate, effectively suppressing αSyn aggregation.[121]

Notably, L-DOPA (levodopa), a BBB-permeable drug used to increase dopamine levels in the brain for the treatment of PD and alleviate motor symptoms, has also been used as a brain-targeting ligand for nanovehicles.[122,123] For example, L-DOPA-functionalized AuNPs can effectively cross the BBB in vitro and be internalized by brain macrophages without causing inflammation, demonstrating potential application as non-inflammatory BBB-penetrating nanocarriers for efficient delivery of therapeutics to the brain.[123] Similarly, liposomes guided by L-DOPA and cholesterol were designed for DNA delivery, ensuring targeted delivery to dopamine neurons of αSyn downregulating genes.[124] These biomimetic NPs exhibited high BBB permeability, evasion of the cellular reticuloendothelial system, and efficient targeting of dopamine neurons. Despite its potential as a ligand for brain-targeted nanomedicines, L-DOPA presents certain challenges that need consideration. The enzymatic metabolism of L-DOPA poses a challenge for sustained and targeted drug delivery. L-DOPA is a precursor to dopamine, and its rapid conversion can occur systemically, reducing the availability of intact L-DOPA for brain targeting. Finally, L-DOPA treatment alleviates motor symptoms but does not slow down or stop neurodegeneration.

Another potential neuroprotective strategy for supporting and protecting neurons in neurological diseases such as PD involves delivering neurotrophic factors (NTF) or NTF-encoding genes to the brain.[29,125,126] Although the clinical potential of NTF has been proven,[97,127] a major obstacle remains the inability of NTF to cross the BBB.[128] To overcome this limitation, NTF delivery via nanocarriers has been explored in recent years.[29] For example, an ultrasound-responsive neurotrophic factor-loaded microbubble-liposome complex was able to improve behavioural impairments and prevent to loss of dopamine neurons in PD mouse model.[53] However, despite ongoing research, available reports on nano-based NTF delivery methods are still limited. Combining NPs with DNA or RNA encoding NTF and decorating these NPs with brain-homing peptides would be very promising. In the case of NTF, it is also important that they reach the brain neurons that naturally secrete NTF.

Despite these advances, challenges persist in the field of brain delivery for neurodegenerative diseases. Achieving optimal drug distribution within the intricate neural networks, addressing the heterogeneity of neurodegenerative diseases, and ensuring the long-term safety of nanomedicines are critical hurdles. The complexity of the BBB and its dynamic nature present challenges in sustaining effective drug concentrations over time. Furthermore, concerns about potential immunogenicity and long-term toxicity associated with nanomaterials call for rigorous investigation and safety assessments.

Future perspectives in brain-targeted nanomedicines for neurodegenerative diseases necessitate innovative solutions. Tailoring nanomedicine formulations to target specific molecular signatures of diseases, employing multifunctional nanocarriers,

and integrating real-time imaging techniques for precise drug tracking represent promising directions. Given that the key targets of modern nanomedicines are amyloid proteins (tau and Aβ) and neuroinflammation, there is an urgent need for new drugs with multi-therapeutic capabilities that could prevent early disease progression, rather than just treat symptoms. Collaborations between interdisciplinary research teams, combining expertise in nanotechnology, neuroscience, and pharmacology, can propel the development of transformative therapies. As nanomedicine continues to evolve, it holds immense potential in reshaping the landscape of neurodegenerative disease treatment, providing hope for improved patient outcomes and quality of life.

Nanomedicine in Brain Cancer

Brain cancers and tumors are another area in which nanomedicines have great therapeutic promise. For example, chemotherapeutic drugs for the treatment of brain tumors suffer from poor bioavailability, insufficient BBB permeability, and a lack of selective targeting, which inevitably leads to low efficacy and systemic toxicity of chemotherapy. Notably, the average life expectancy for patients with glioblastoma, the most common form of brain cancer, is less than 2 years.[129] Despite the widespread observation of brain-impenetrant contrast material accumulation in high grade gliomas, the clinical data consistently reveals a significant tumor burden in brain tumors with an intact BBB.[130] Consequently, drugs with poor BBB permeability fail to achieve therapeutically effective exposures in these tumor regions and new drug delivery strategies are needed to achieve more efficient therapeutic effects against brain tumors.

To target both the BBB and blood-brain tumor barrier, nanostructured dual-targeting lipid carriers were developed to deliver Bortezomib, a proteasome inhibitor anti-cancer agent. Specifically, the surface of targeted NPs modified with BBB-targeting 8-residue D-peptide and RI-VAP ligand of glucose-regulated protein 78 (GRP78), with superior glioma-homing property, could simultaneously cross the BBB and the blood-brain tumor barrier with high efficiency and target the glioma cells with excellent selectivity in vitro and in vivo.[131] Another dual-modified liposomes for anti-cancer drug delivery (doxorubicin) were developed via surface-functionalization by glucose and mitochondria-targeting ligand triphenylphosphonium.[132] Designed NPs demonstrated excellent targeting and internalization ability for tumor cells, endo/lysosomal escape and superior mitochondria targeting capability.

Angiopep-2 is being actively explored as a brain-targeting ligand for anti-glioma nanomedicines.[133–139] For example, polymeric NPs, featuring dual surface modification with Angiopep-2 and L-histidine to facilitate BBB-to-glioblastoma transport and endosomal escape, successfully delivered the docetaxel drug to glioblastoma, resulting in ~12-fold increase in tumor cell uptake (Figure 4A).[140] Furthermore, a biomimetic nanomedicine was created using Angiopep-2 peptide-decorated red blood cell membranes and pH-sensitive dextran NPs for the targeted delivery of Navitoclax (anti-cancer drug) and the inducer of myeloid leukemia cell differentiation protein-specific inhibitor A-1210477 to the brain.[141] This nanomedicine demonstrated effective BBB penetration and successfully inhibited tumor growth, leading to prolonged survival in mice (Figure 4B). Similarly, gold surface-coated iron titanium-shell NPs conjugated with Angiopep-2 exhibited outstanding brain-targeting capabilities and applicability for magnetic resonance imaging.[142] In another study, Angiopep-2 modified liposome-silica hybrid nanovehicles functionalized with polyacrylic acid (pH-sensitive release) and loaded with arsenic trioxide (ATO, glioma drug) achieved targeted delivery and on-demand release of ATO for brain glioma therapy (Figure 4C).[137] A similar but ROS-responsive and Angiopep-2-targeted siRNA delivery system was developed by Zheng et al.[135] This BBB-permeable polymeric siRNA nanomedicine stabilized by triple interactions (electrostatic, hydrogen bond, and hydrophobic), showed efficient release of siRNA resulting from tumor-derived ROS triggered sequential destabilization of the nanocarrier. In addition, siRNA against epidermal growth factor receptor and programmed cell death ligand-1 for combined targeted and immunotherapy against glioblastoma was delivered using radiation-induced targeted NPs.[143] A short burst of radiation therapy enhanced the uptake of NPs by glioblastoma cells, resulting in activation of immune response, inhibition of tumor growth, and increased survival of mice.

Transferrin and affinity ligands targeting its receptor have also been investigated as targeting ligand in anticancer nanomedicines. For instance, PEGylated NPs functionalized with transferrin and loaded with temozolomide revealed enhanced BBB penetration and glioblastoma targeting ability in vivo.[83] Similarly, transferrin-modified and asiatic acid-loaded poly(lactic-co-glycolic acid) NPs showed increased selectivity of NPs toward glioblastoma cells by enhancing their uptake through the transferrin-mediated endocytosis mechanism.[144] transferrin. Earlier, Kim et al demonstrated that temozolomide-loaded liposomes modified with anti-transferrin single-chain variable fragments can deliver tumor suppressor p53 gene to limit chemoresistance and prolong survival in a mouse model of glioblastoma.[145] p53 inhibits DNA-repair protein O6-methylguanine-DNA

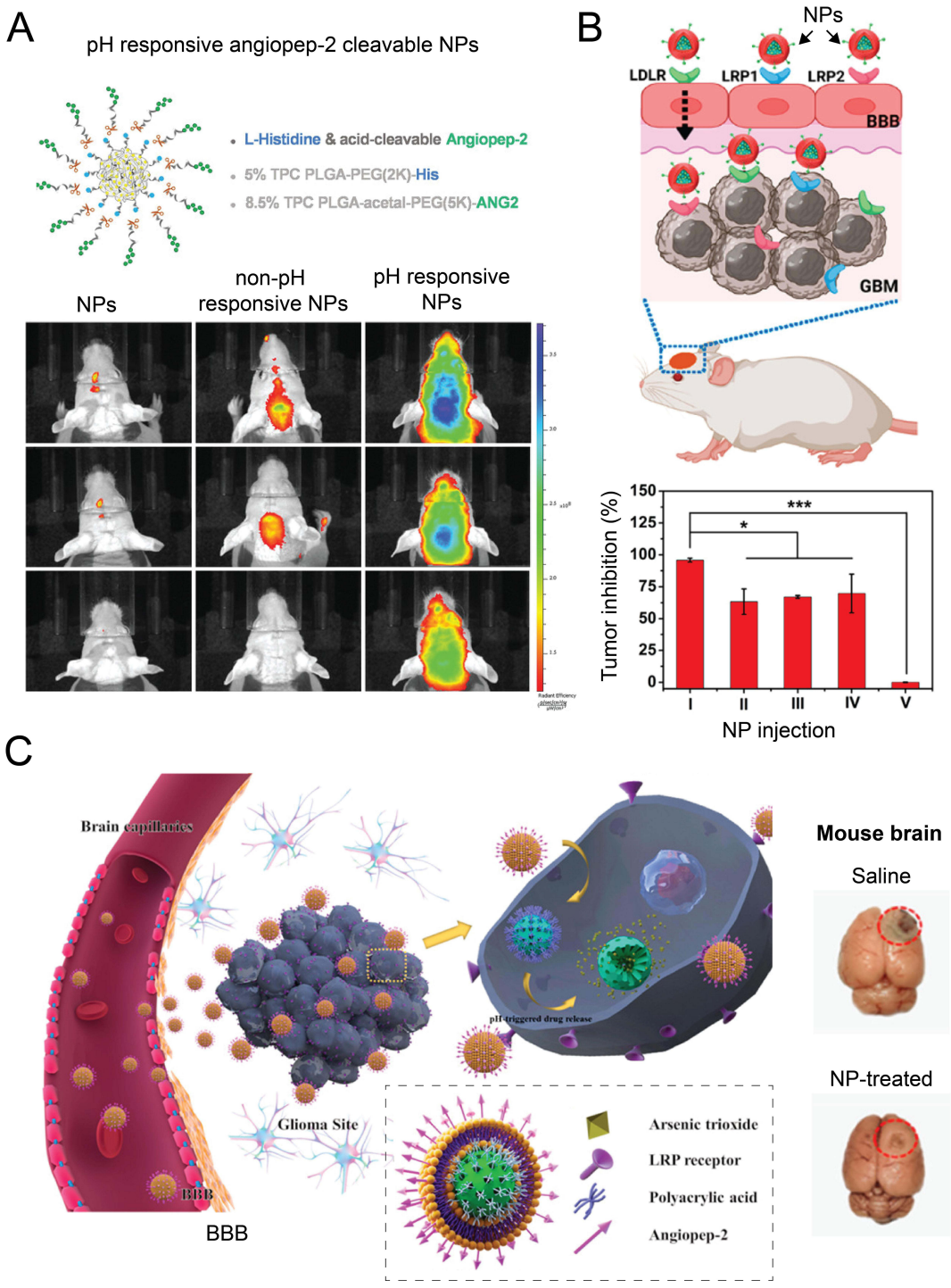

Figure 4 Application of brain-targeted nanomedicines for brain cancer. (**A**) L-histidine (His) functionalized and pH-responsive acid-cleavable angiopep-2 (ANG2) NPs showed superiors BBB-permeability and brain accumulation in comparison to non-functionalized or non-cleavable NPs. Adapted from Martins C, Araújo M, Malfanti A, et al. Stimuli-Responsive Multifunctional Nanomedicine for Enhanced Glioblastoma Chemotherapy Augments Multistage Blood-to-Brain Trafficking and Tumor Targeting. *Small*. 2023;19(22):2300029. © 2023 The Authors. Small published by Wiley-VCH GmbH.[140] (**B**) Schematic illustration of the biomimetic nanomedicine penetrating the BBB and targeting the tumor site via the specific recognition of apolipoprotein E peptide and the multiple low-density lipoprotein receptor (eg, LDLR, LRP1, and LRP2) overexpressed in the BBB endothelial cells and glioblastoma (GBM) cells (upper). Evaluation of the tumor inhibition rate after five successive injections of NPs (bottom). Data are presented as the mean ± SD (*$p < 0.05$ and ***$p < 0.001$). Adapted from He W, Li X, Morsch M, et al. Brain-Targeted Codelivery of Bcl-2/Bcl-xl and Mcl-1 Inhibitors by Biomimetic Nanoparticles for Orthotopic Glioblastoma Therapy. *ACS Nano*. 2022;16(4):6293–6308. Copyright © 2022 American Chemical Society.[141] (**C**) Angiopep-2-conjugated hybrid nanovehicles targeted glioma cells and delivered arsenic trioxide reducing necrosis of tumor tissue in the brain. Reprinted from Tao J, Fei W, Tang H, et al. Angiopep-2-conjugated "core–shell" hybrid nanovehicles for targeted and pH-triggered delivery of arsenic trioxide into glioma. *Mol Pharm*. 2019;16(2):786–797. Copyright © 2019 American Chemical Society.[137]

methyltransferase activity which can repair DNA damage caused by temozolomide, reversing the therapeutic effects.[146] Notably, this is the only anti-glioblastoma drug delivery system using transferrin to reach clinical stage (ClinicalTrials.gov Identifier: NCT02340156).

Conjugation with tumor-homing peptides can also increase tumor tropism and antitumor therapeutic efficacy of NPs. For example, clinical-stage tumor penetrating peptide iRGD that accumulates in vascular endothelial cells and tumor cells positive for expression of angiogenic integrins and Neuropilin-1,[68] has been demonstrated to increase glioma accumulation and preclinical therapeutic efficacy of several nanosystems including temozolomide-loaded polyhedral oligomeric silsesquioxane NPs,[147] tirapazamine and zinc phthalocyanine NPs,[148] and NIR-II phototheranostics.[149] Whereas iRGD is known as a generic solid tumor homing peptide, in brain tumors it has the added value of facilitating the NP penetration of the BBB.[150] Beyond iRGD, several other tumor homing peptides have demonstrated effectiveness in NP delivery to glioma lesions. Examples include the LinTT1 peptide, which targets Neuropilin-1, and p32, enhancing glioma homing of iron oxide nanoworms and albumin-paclitaxel NPs across a spectrum of glioblastoma models, ranging from infiltratively-disseminating to angiogenic phenotypes.[151] Recently, silica NPs functionalized with the cell penetrating TAT peptide demonstrated promising outcomes in delivering the chemotherapeutic agent methotrexate to the brain.[152] Additionally, the extracellular matrix-targeting PL1 peptide has shown engagement with tumor-associated isoforms of extracellular matrix molecules Tenascin C and Fibronectin in glioblastoma models.[153] These peptides contribute to the advancement of targeted drug delivery strategies for various glioma subtypes. To enhance tumor specific delivery, cyclo(-Arg-Gly-Asp-D-Phe-Cys) peptide was used as the targeting ligand specific to tumor integrin $\alpha_v\beta_3$ overexpressed on angiogenic endothelial cells in the tumor vasculature.[154] Iron oxide NPs conjugated with this tumor-specific peptide exhibited an impressive tumor delivery 11.5%ID/g of a water-insoluble DNA topoisomerase I inhibitor, resulting in over 40% inhibition of tumor growth.

Effective therapy for brain tumors in general remains a medical challenge and requires concentrated research efforts. The development of multitarget drugs for the treatment of glioblastoma remains a very promising therapeutic approach. However, despite notable progress and advancements, challenges persist in brain cancer nanomedicine. One important contributing factor that applies to affinity targeting ligands may be the limited capacity of receptors in the target tissue, imposing constraints on the number of conjugates that can home to the target.[155] Once these receptors are saturated, the specific delivery plateaus, and off target effects ensue due to the presence of remaining conjugates circulating in the system. In tumors, this problem may be further compounded by inadequate drug penetration. iRGD peptide, and potentially other tumor penetrating C-end Rule peptides, may provide a path around this limitation to achieve precision drug delivery at therapeutically relevant concentrations.[156] In addition, overcoming the heterogeneity of brain tumors, improving drug release kinetics, and ensuring sustained efficacy remain focal points. Future perspectives involve refining targeting ligands, exploring combination therapies, and leveraging emerging technologies like artificial intelligence for personalized treatments. Collaborative efforts among researchers, clinicians, and industry partners will be pivotal in realizing the full potential of brain-targeted nanomedicines for enhanced brain cancer therapy.

Nanomedicine for Stroke Treatment

A stroke is a severe and acute brain condition that can result in disability and death. Strokes are broadly categorized into two main types: hemorrhagic and ischemic. Hemorrhagic stroke results from bleeding caused by the rupture of a blood vessel in the brain and is associated with severe morbidity and high mortality.[157] An ischemic stroke is a critical and sudden brain condition that can result in disability and death. It is marked by a sudden reduction in cerebral blood flow caused by an obstruction in the cerebral blood vessels, leading to damage to nerve tissue.[158] Lack of blood flow causes brain cell dysfunctions, oxidative stress, and neurological damage.[159] Dead neuronal cells release damage-associated molecular patterns that activate the innate and adaptive immune systems, triggering inflammatory pathways. Although BBB is compromised in stroke, the BBB opening is heterogeneous and stroke treatment has limitations due to poor ability to deliver therapeutic agents.[160] Therefore, efforts have been made to develop new brain-targeted drug delivery methods. Recently, nanotechnology emerged as an innovative drug delivery tool to improve the treatment of ischemic stroke. Most research has focused on the treatment of ischemic stroke, as it is the most common form of the disease in Europe and America but not in Asia.[161] Treatment of ischemic stroke aims to quickly restore blood flow to the brain and is an important strategy to protect neurological damage.[162] Neuroprotective approaches include reducing immune cell adhesion, blocking of proinflammatory cytokines, reducing lipid peroxidation, and decreasing cell apoptosis. NP-drug delivery systems have been developed to overcome the short plasma half-life time and low BBB permeability of anti-stroke drugs.

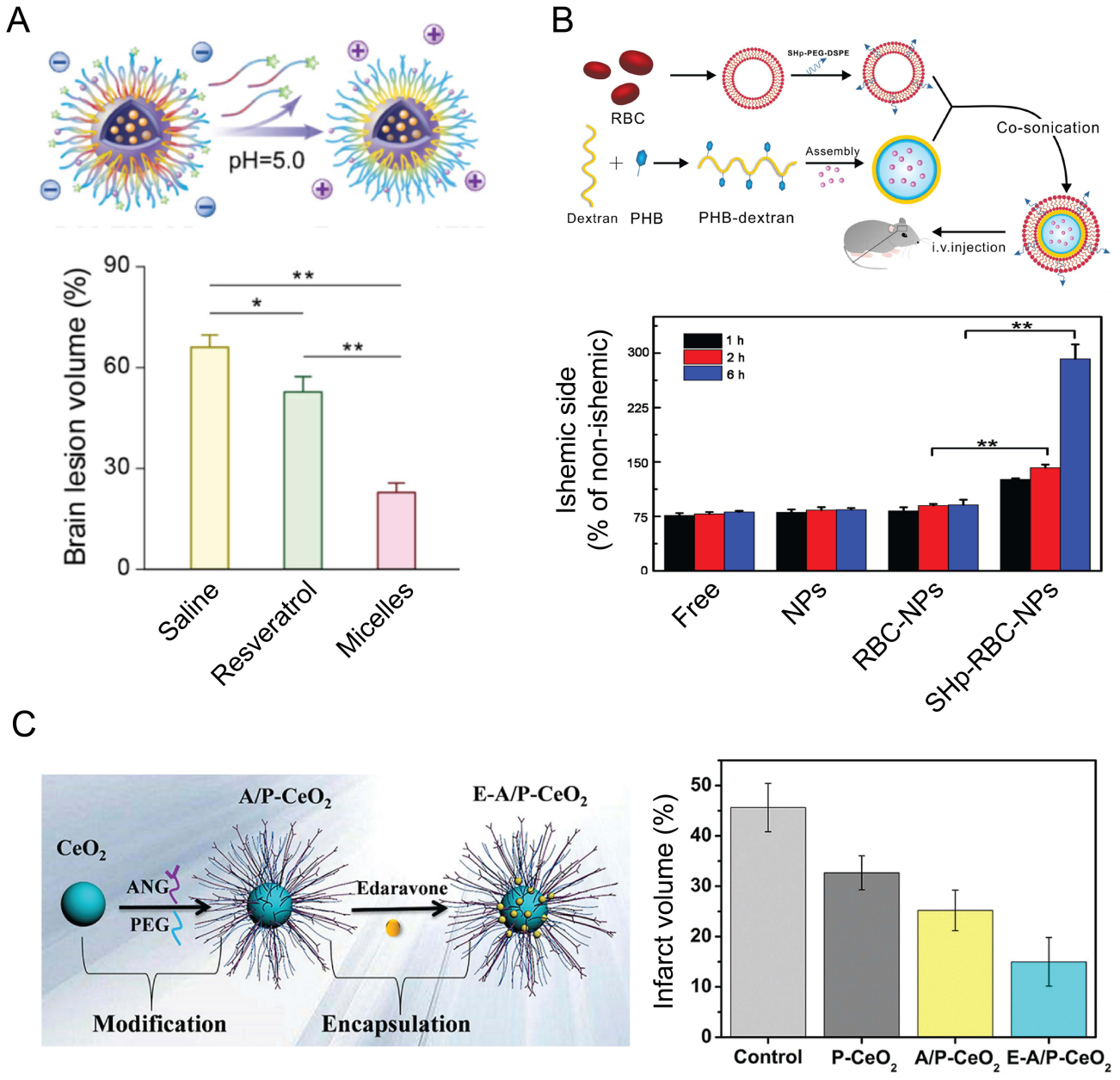

Figure 5 Brain-targeted nanomedicines against stroke. (**A**) Schematic illustration of brain-targeted micelles releasing a long PEG chain to expose triphenylphosphine at pH 5.0 (upper). By T2-weighted magnetic resonance imaging (MRI), the recovery of brain injury was remarkably enhanced after treatment with resveratrol-loaded micelles, reducing the infarct area by 65.7% than in the saline group (bottom). Adapted from Wang Z, Pan J, Yuan R, Chen M, Guo X, Zhou S. Shell-Sheddable Polymeric Micelles Alleviate Oxidative Stress and Inflammation for Enhanced Ischemic Stroke Therapy. *Nano Lett*. 2023;23(14):6544–6552. Copyright © 2023 American Chemical Society.[163] Data are presented as mean ± SD. One-way ANOVA was used to calculate P values (*P < 0.05, **P < 0.01, ***P < 0.001). (**B**) The nanocarrier composed of a dextran polymer core modified with ROS-responsive boronic ester (PHB) and a red blood cell (RBC) membrane shell with stroke homing peptide (SHp) inserted (scheme design upper panel), enhance targeting of ischemic area and reduce ischemic brain damage (lower panel). Adapted from Lv W, Xu J, Wang X, Li X, Xu Q, Xin H. Bioengineered boronic ester modified dextran polymer nanoparticles as reactive oxygen species responsive nanocarrier for ischemic stroke treatment. *ACS nano*. 2018;12(6):5417–5426. Copyright © 2018 American Chemical Society.[164] Statistical analysis used one-way ANOVA test (**P < 0.01). (**C**) Ceria NPs, which were loaded with edaravone and modified with Angiopep-2 and PEG on their surface (E-A/P-CeO2), demonstrated great intracephalic uptake, and ability to prevent the injuries on both brain tissues and BBB in strokes. Adapted from Bao Q, Hu P, Xu Y, et al. Simultaneous blood–brain barrier crossing and protection for stroke treatment based on edaravone-loaded ceria nanoparticles. *ACS Nano*. 2018;12(7):6794–6805. Copyright © 2018 American Chemical Society.[165]

To tackle this challenge, Wang et al innovatively crafted polymeric micelles with surface modification using cyclo(Arg-Gly-Asp-d-Tyr-Lys) peptide, enabling efficient BBB penetration via transcytosis.[163] Additionally, these micelles incorporated triphenylphosphine for mitochondria targeting. This acid-responsive formulation effectively mitigates oxidative stress and inflammation by enhancing the delivery of resveratrol to microglia mitochondria, thereby reversing the microglia phenotype through the scavenging of ROS for the treatment of ischemia-reperfusion injury (Figure 5A). To target ischemic brain, Lv et al

designed ROS-responsive boronic red blood cell membrane shell polymeric NPs decorated with stroke homing peptide (SHp) for delivery of a neuroprotective agent NR2B9C.[164] These bioengineered NPs improved neuroscores and infarct volume in response to surgical middle cerebral artery occlusion injury, reducing ischemic brain damage (Figure 5B). Angiopep-2 is also studied as a ligand to guide stroke medicines aggress the BBB. For instance, Angiopep-2 conjugated to PEGylated edaravone-loaded ceria NPs, mediated BBB transcytosis and ROS-scavenging effect (Figure 5C). [165] Edaravone-loaded ceria NPs could not only enhance the intracephalic uptake but also prevent the injuries on both brain tissues and BBB in strokes.

The search for new therapeutic strategies for the treatment of stroke has increased significantly, and combining these treatments with the effective solutions offered in the field of nanotechnology will help in finding new effective therapeutics to improve the outcome of stroke patients. However, despite the success of improving stroke therapy with various nanomedicines in preclinical studies, none of these systems have yet been used to benefit patients. Looking ahead, a multifaceted approach integrating advances in nanotechnology, targeted ligands, and formulation engineering, alongside a deeper understanding of the complex biology of stroke, holds the key to unlocking the full potential of brain-targeted nanomedicine for stroke treatment.

Conclusion and Perspectives

Targeting drugs to the brain is one of the most challenging problems in pharmaceutical research due to the highly selective permeability of the BBB. Obstacles encountered in drug delivery to the brain have been significantly improved by recent developments in drug targeting techniques. In addition, high therapeutic drug concentrations in the brain must be achieved through an effective and safe carrier. Thus, there is a need for good vehicles that deliver the drug across the BBB at an effective concentration without causing systemic side effects. Nanomedicines have been implicated in solving problems associated with targeted drug delivery for the treatment of neurological disorders. Different classes of nanomaterials have been explored as drug nanocarriers across the BBB, and various targeting ligands have shown great promise for drug delivery to the brain. Notably, targeting ligands, such as peptides and antibodies, have shown substantial promise in enhancing the specificity of drug delivery to the brain. The ongoing exploration and refinement of nanotechnology in conjunction with efficient brain-targeting methods hold immense potential to reshape our therapeutic approach to neurological disorders.

However, it is imperative to critically analyze the existing situation and acknowledge persisting challenges. The immunogenicity and potential toxicity of nanocarriers demand meticulous scrutiny and continuous refinement to ensure the safety of these innovative drug delivery systems. Additionally, the heterogeneity of neurological disorders further complicates drug design and requires a detailed understanding of the unique challenges associated by each condition. Future directions in the field should focus on developing personalized and disease-specific nanomedicines, tailoring formulations to the distinctive characteristics of various neurological disorders.

Translating successful results of brain-targeted nanomedicine from preclinical settings to clinical applications is a challenging task, requiring the collaborative efforts of multidisciplinary teams to overcome the complexities of human physiology. Although some nanomaterials have received FDA approval or entered clinical trials, practical implementation of brain-targeted nano-based drug delivery systems in clinical settings remains very limited. This highlights the complex process of moving from laboratory success to widespread clinical use, requiring innovative strategies to optimize this translational process. The complex nature of the blood-brain barrier, interindividual variability in patient responses, and the need for precision in drug delivery mechanisms present significant obstacles. Ethical considerations, safety concerns, and the exorbitant cost of clinical trials are also contributing to a cautious approach to using brain-targeted nanomedicines on a larger clinical scale.

In addressing these challenges, the integration of advanced imaging techniques and the identification of reliable biomarkers is critical. These methodologies offer valuable information on the pharmacokinetics and biodistribution of nanomedicines in the human brain, providing the basis for informed and effective clinical strategies. Despite the complexity of these obstacles, ongoing research initiatives and collaborative efforts provide optimism that these challenges can be overcome and brain-targeted nanomedicines will be widely implemented in clinical practice in the foreseeable future.

In the years ahead, interdisciplinary collaboration, rigorous safety assessments, and a deepened understanding of the intricacies of neurological disorders will be essential to successfully realize the potential of nanotechnology in brain-targeted therapies. The evolving field of nanomedicine for brain disorders holds the promise of not only overcoming current challenges but also opening new frontiers in precision medicine, ultimately transforming the prognosis and treatment paradigms of a variety of brain-related diseases.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Mart Saarma (MS) is the founder and a shareholder in Herantis Pharma Plc. that develops PD drugs. MS is also a shareholder in Nanoform Plc that develops new nanotechnologies. Tambet Teesalu is an inventor on patents on CendR peptides and a shareholder of Lisata Therapeutics, a company that develops tumor-penetrating CendR peptides for cancer therapy. The authors report no other conflicts of interest in this work.

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