Nanomedicine for Neurological Disorders: Advanced Nanotherapeutic Strategies, Blood–Brain Barrier Targeting, and Translational Perspectives

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ABSTRACT

Diseases of the nervous system, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, stroke, glioblastoma and traumatic brain injury, continue to be important causes of disability and death around the world. However, the effectiveness of conventional therapies is often hampered by poor solubility, systemic toxicity, and fast metabolism and by limited transport across the blood–brain barrier (BBB). Nanomedicine has come up as a novel treatment modality that can overcome these limitations by targeted delivery, controlled release, improved drug bio-availability and precision treatment. It summarizes the design and biomedical applications of lipid nanoparticles, polymeric nanoparticles, dendrimers, liposomes, exosomes, nanogels, magnetic nanoparticles and biomimetic nano-carriers in the field of neurological disorders in a comprehensive manner. A special attention is given to BBB-targeting strategies, receptor-mediated transport, stimulus-responsive nanoplatforms, neuroprotective therapeutics and nanotheranostic systems, involving simultaneous diagnosis and therapy. Current clinical evidence, regulatory issues and future prospects for emerging developments in AI-driven nanotechnology design, personalized nanomedicine and translational research are critically discussed in this chapter.

Keywords; Nanomedicine; Neurological Disorders; Blood–Brain Barrier; Nanoparticles; Targeted Drug Delivery; Neurodegeneration

INTRODUCTION

Neurological disorders are one of the largest and fastest growing public health problems in the world. These conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), stroke, glioblastoma, epilepsy, and traumatic brain injury are all on the rise globally due to ageing populations and advances in diagnosis. These disorders are a major contributor to disability adjusted life years (DALYs) and mortality in all socioeconomic groups, have high costs to health systems and significantly affect people's quality of life [1,2].

Although many years of intense research have been conducted, there are significant challenges for traditional therapeutic strategies in neurological disorders. Small molecule drugs suffer from low aqueous solubility, high metabolic clearance rate, toxicity at therapeutic doses and low bioavailability when administered orally. The blood–brain barrier (BBB) is the major barrier to the uptake of > 98% of small molecule drugs and essentially all macromolecular therapeutics into the central nervous system (CNS) [3], making the traditional delivery of

drugs via systemic administration largely ineffective for CNS targets. This barrier is crucial for the normal function of the CNS but is the most important obstacle to successful neurological drug therapy.

The need for these basic challenges has been met with the advent of a new paradigm: nanomedicine [4,5]. Nanomedicine involves engineering materials at the nanoscale (between 1-1000 nm) and allows the rational design of drug delivery systems with well controlled physicochemical parameters. Nanocarriers are able to encapsulate therapeutic agents and prevent them from being degraded prematurely, protect from their solubility and allow sustained or triggered release profiles. In addition, surface functionalization with targeting ligands can be used to achieve homing to diseased tissues, and proper surface engineering can be used to control pharmacokinetics and biodistribution. The exciting combination of nanotechnology with molecular biology and materials science have opened up brand new possibilities of precision medicine in neurology [6].

The overall objective of this comprehensive chapter is to systematically describe the current landscape of nanomedicine for neurological disorders, covering everything from the basics of designing nanocarriers, targeting the BBB, the disease-specific applications, theranostic strategies, and the challenges towards translation. It covers from basic physicochemical aspects to clinical translation, highlighting the new technologies such as artificial intelligence for design, biomimetism, and individual nanomedicine.

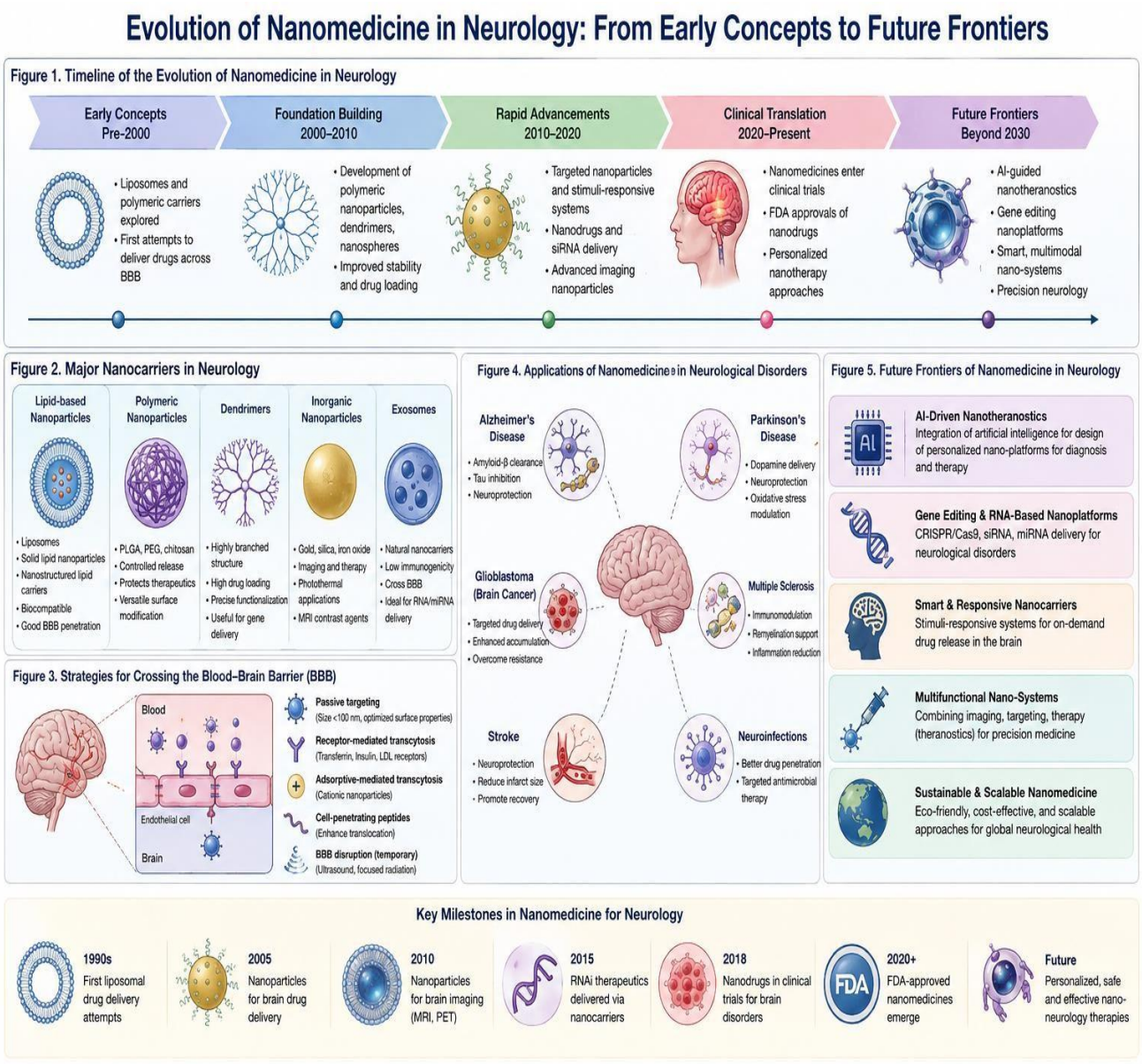


Figure 1: Evolution of nanomedicine in neurology.

PATHOPHYSIOLOGY OF NEUROLOGICAL DISORDERS

Although these are all distinct diseases of the nervous system, there are some common mechanisms shared by these diseases that are exciting therapeutic targets for nanomedicine-based therapies [7, 8].

Neuroinflammation is a common pathological mechanism in all neurological diseases. Injury, protein aggregates and autoimmune processes activate microglial and astrocytes and release pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), chemokines and reactive oxygen species (ROS). Chronic neuroinflammation has initially neuroprotective properties but it may sustain the damage to the neurons and is part of the disease process [9]. The activation of Toll-like receptors and the NLRP3 inflammasome by amyloid-β plaques and neurofibrillary tangles in Alzheimer's disease act as a mechanism of microglial activation. The activation of Toll-like receptors and the NLRP3 inflammasome by amyloid-β plaques and neurofibrillary tangles in Alzheimer's disease is a mechanism for microglial activation. This aggregation of α-synuclein also causes microglial activation in Parkinson's disease. In MS, the demyelination and damage to the axon results from autoimmune mediated inflammation. The ability of nanomedicine to selectively target activated microglia and astrocytes to deliver an anti-inflammatory agent may dampen neuroinflammatory cascades without impacting peripheral immune function.

Oxidative stress occurs when there is an imbalance between the production of ROS and antioxidant defense. The brain is especially susceptible to oxidative damage because it has high levels of oxygen consumption, rich in polyunsaturated fatty acids, and with relatively low levels of antioxidants [10]. Impaired electron transport chain function and opening of the mitochondrial permeability transition pore are two mechanisms by which mitochondrial dysfunction in neurodegenerative disorders contributes to an increase in ROS production. The nanocarriers responsive to ROS are a promising approach to controlling drug release only at oxidative damage sites.

There are many different neurodegenerative diseases that involve the aggregation of proteins: amyloid-β plaques and tau tangles in Alzheimer's disease; α-synuclein Lewy bodies in Parkinson's disease; SOD1 and TDP-43 aggregates in ALS; and huntingtin aggregates in Huntington's disease [11]. Nanocarriers may be used to deliver chaperone proteins, autophagy enhancers or aggregation inhibitors to the affected neurons.

Synaptic dysfunction is characterized as defects in neurotransmitter secretion, defects in receptor trafficking, and synaptic loss. Neurotrophic factors (e.g., BDNF, GDNF) can be delivered to maintain and increase synaptic maintenance and plasticity via nanocarriers [12].

There is a critical convergence of mitochondrial dysfunctions in neurodegeneration. MTNCs have the promise to transport antioxidants and mitochondrial biogenesis stimulators [13].

Blood–brain barrier is impaired in both acute and chronic neurological diseases, which may create possibilities for improved penetration by nanoparticles.

Table 1: Major molecular mechanisms involved in neurological diseases.

Mechanism	Key Features	Associated Disorders	References
Neuroinflammation	Microglial activation, cytokine release, chronic inflammation	AD, PD, MS, TBI, stroke	[7,8,9]
Oxidative stress	ROS/RNS production, lipid peroxidation,DNA damage	AD, PD, ALS, stroke, TBI	[10,13]
Mitochondrial dysfunction	Impaired ATP production, ROS generation, apoptosis	AD, PD, ALS,Huntington's	[13]
Protein aggregation	Amyloid-β, tau, α-synuclein, SOD1, TDP-43 aggregates	AD, PD, ALS,Huntington's	[11]
Synaptic	Impaired neurotransmission, synaptic loss	AD, PD	[12]

dysfunction			
BBB impairment	Tight junction disruption, increased permeability, neurovascular unit dysfunction	AD, stroke, TBI, MS	[3,14,15]

BLOOD–BRAIN BARRIER: THE MAJOR THERAPEUTIC CHALLENGE

The blood–brain barrier (BBB) is an especially restricted neurovascular unit, which tightly controls molecule supply between the peripheral blood and the CNS parenchyma. Brain microvascular endothelial cells linked together by tight junctions, a basement membrane, pericytes and astrocytic end-feet are responsible for the structural integrity of the BBB [3].

Structural Organization: Brain endothelial cells have no fenestrations and have few pinocytotic vesicles, but large tight junctions, made up of claudin-5, occludin, and zonula occludens (ZO-1) proteins [14]. The transcellular route is limited by the presence of efflux transporters, such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) [15].

Specific transport systems expressed in the BBB are GLUT1 for glucose, LAT1 for amino acids, and receptor-mediated transcytosis (RMT) through transferrin receptor (TfR), insulin receptor, and LDL receptor-related protein (LRP) [16]. Adsorptive-mediated transcytosis (AMT) is a process in which the electrostatic interactions between the negatively charged glycocalyx and the cationic molecules drive the active transport of the molecules across the cell membrane [17].

The BBB has several sequential barriers to drug delivery: the ability to escape recognition by the RES, pass through the endothelial cell layer, avoid efflux transport, pass through brain parenchyma, and reach intracellular concentrations high enough to be effective [18].

The following strategies have been suggested to overcome the BBB: receptor-mediated transcytosis with the help of targeting ligands [19] temporary BBB disruption using focused ultrasound with microbubbles [20] intranasal administration without BBB [21] cell-penetrating peptides [22] optimization of nanoparticle surface properties.

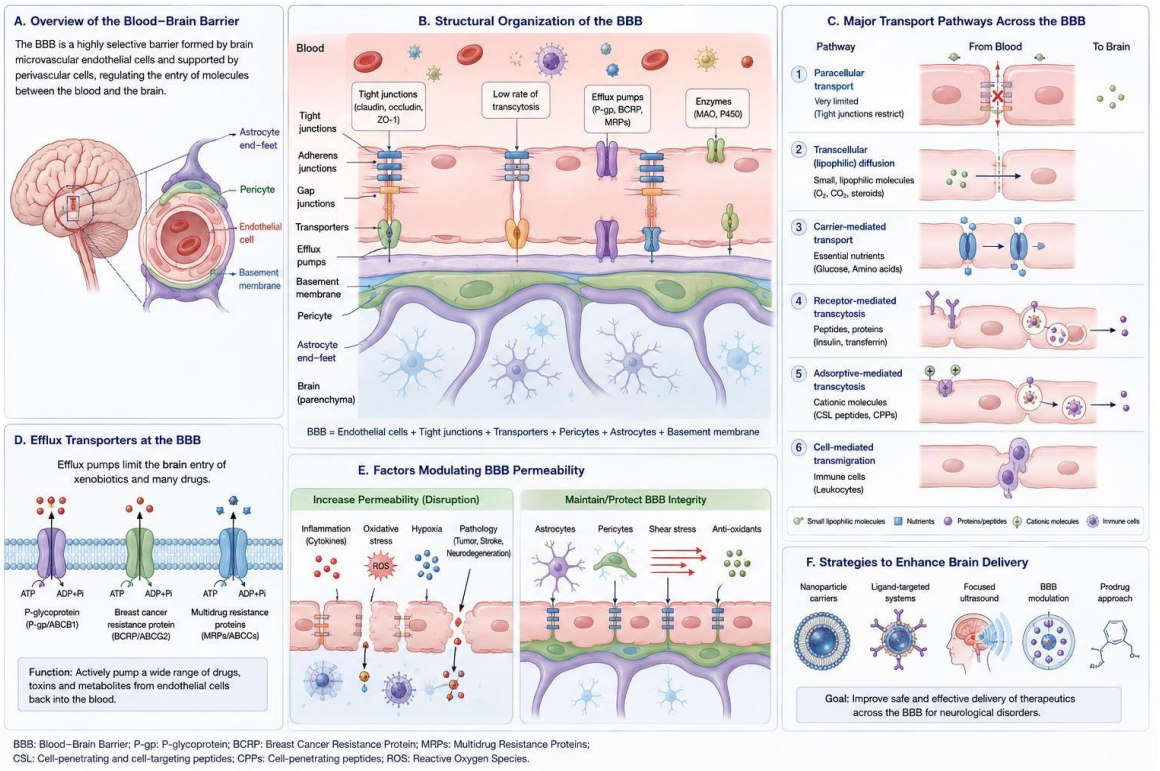


Figure 2: Structure and transport pathways across the BBB.

FUNDAMENTALS OF NANOMEDICINE (500 WORDS)

Nanomedicine is the design, synthesis and utilization at the nano size (1–1000 nm) of materials for diagnostic and therapeutic applications [4].

There are several types of Nanomaterials: Organic nanocarriers such as liposomes, polymeric nanoparticles, lipid nanoparticles, dendrimers, polymeric micelles and nanogels. Gold nanoparticles, magnetic nanoparticles, silica nanoparticles and carbon nanomaterials are considered as inorganic nanocarriers. The hybrid nanoparticles are nanoparticles composed of both organic and inorganic elements [23].

Biodistribution, cellular uptake and penetration of the BBB are influenced by the physicochemical properties of the nanocarriers, such as particle size (optimal range of 10–100 nm for brain accumulation [24]), surface charge and surface chemistry. The effect of PEGylation on pharmacokinetics and immunogenicity is modified [25].

The benefits over conventional therapeutics include: protection from degradation, increased solubility, controlled delivery, targeting, codelivery of multiple agents, theranostic integration, crossing of the BBB [26]. Safety: Possible toxicity can be attributed to oxidative stress, inflammation, mitochondrial dysfunction and genotoxicity [27]. Protein corona formation, immune recognition and RES clearance impact both safety and efficacy [28].

NANOCARRIERS FOR NEUROLOGICAL DRUG DELIVERY

Liposomes

The liposomes are spherical vesicles made up of phospholipid bilayers. They are biocompatible, can be used for hydrophilic/lipophilic drug encapsulation, can be modified with surface targeting, and can be PEGylated for extended circulation for CNS applications [29]. Formulations for Alzheimer's disease, Parkinson's disease, MS, stroke and glioblastoma have been developed in the form of liposomes [30]. Two liposomal vaccines, ACI-24 and ACI-35.030, are now in clinical trials [31].

Polymeric nanoparticles

Polymeric nanoparticles (PNPs) made of PLGA, PLA, or chitosan provide controlled release, high loading of drugs, and versatility of surface functionalization [32]. Brain targeting has been shown to be better with transferrin as a targeting agent for PLGA nanoparticles [33]. The polymeric nanoparticles loaded with rotigotine (POZ-rotigotine) are now in clinical investigation [34].

Lipid nanoparticles

The SLNs and nanostructured lipid carriers (NLCs) have the benefits of both liposomes and polymeric nanoparticles [35]. Surface modification with a polysorbate 80 helps apolipoprotein E to bind for LDL receptor mediated BBB transport [36].

Dendrimers

Dendrimers are macromolecules with a defined molecular weight and surface functional groups which have a very high degree of branching and monodispersity [37]. In the models of neuroinflammation, hydroxyl-terminated PAMAM dendrimers exhibit increased brain uptake [38].

Exosomes

Exosomes are naturally occurring extracellular vesicles (30–150 nm) which are naturally biocompatible, have BBB crossing capability and potential for targeted delivery [39].

Synergistic neuroprotection is now found in a new exosome-liposome hybrid system [40].

Nanogels

Nanogels are highly water containing particles consisting of crosslinked hydrogels, allowing the release of the drug in response to the stimuli [41]. Nanogels that are glucose responsive have been studied for use in stroke and ischemia [42].

Magnetic nanoparticles

Magnetic nanoparticles (iron oxide) can be used to guide drug delivery using magnetic field and as contrast agents for MRI [43]. Doxorubicin and paclitaxel were shown to be effective in inhibiting the growth of glomas when transferred to magnetic silica PLGA nanoparticles, coated with transferrin [44].

Biomimetic nanoparticles

The biomimetic nanoparticles are based on cell membranes to ensure a natural targeting and immune evasion [45]. Artificial apolipoprotein coronas provide a model for endogenous lipoprotein transport and can be used to target the BBB [46].

Table 2: Comparison of Nanocarriers for CNS Drug Delivery.

Nano carrier	Size (nm)	Drug Loading Capacity	BBB Targeting Capability	Crossing Mechanism	Advantages	Limitations	Clinical Status	References
Liposomes	50–200	High (hydrophilic & lipophilic)	Yes (ligand conjugation)	RMT/AMT	Biocompatible, clinically validated, versatile	Limited stability, rapid RES clearance	FDA-approved (non-CNS); Clinical for CNS	[26,29,30]
Polymeric NPs	50–300	High	Yes	RMT/AMT	Controlled release, tunable degradation	Polymer toxicity, batch variability	Clinical	[32,33,34]
Lipid NPs (SLN/NLC)	50–400	Moderate to high (lipophilic)	Yes (with surface modification)	RMT/AMT	Excellent biocompatibility, scalable	Limited hydrophilic drug loading	Clinical	[35,36]
Dendrimers	10–20	High	Yes (multivalent)	AMT	Monodisperse, precise molecular control	Complex synthesis, potential toxicity	Preclinical	[37,38]
Exosomes	30–150	Moderate	Natural	Natural BBB crossing	Endogenous biocompatibility, low immunogenicity	Limited loading, batch variability	Preclinical	[39,40]
Nanogels	20–200	High (hydrophilic)	Yes	AMT	Stimulus-responsive, high water content	Limited mechanical stability	Preclinical	[41,42]
Magnetic NPs	10–100	Moderate	Yes (magnetic field)	Magnetic field guidance	Theranostic potential, hyperthermia	Iron toxicity, limited loading	Preclinical	[43,44]
Biomimetic NPs	50–200	High	Natural (cell membrane)	Natural cell membrane proteins	Immune evasion, natural targeting	Complex fabrication, batch variability	Preclinical	[45,46]

DISEASE-SPECIFIC APPLICATIONS

Alzheimer's disease

Amyloid-β plaques, tau tangles, neuroinflammation and synaptic loss are evidence of Alzheimer's disease. There is no symptomatic benefit with present therapies [47]. A variety of drugs, including anti-amyloid agents, anti-tau agents, anti-inflammatory drugs, neuroprotective factors and delivery of siRNA, have been engineered

using nanoparticles [48]. Both liposomal vaccines (ACI-24 and ACI-35.030) are currently in Phase I/II clinical trials [31].

Parkinson's disease

In Parkinson's disease, there is a loss of dopaminergic neurons and aggregation of α-synuclein. Nanoparticles are used to provide dopamine agonists (rotigotine, bromocriptine), GDNF, aggregation inhibitors of α-synuclein and anti-inflammatory agents. LY-03003 (rotigotine micro particles) is in Phase III clinical trials [34].

Multiple sclerosis

MS is an autoimmune disease that affects the myelin. The immunosuppressive agents, the agents for restoring neural function and the antigen-specific immunomodulators are delivered to the recipient via nanoparticles. There are clinical trials underway of liposomal vaccines Xemys and Myeloxen [49].

Stroke

Neuroprotection and rapid thrombolysis are important for the treatment of stroke. Thrombolytic agents, Neuroprotective agents (edaravone), anti-inflammatory agents are delivered by nanoparticles. Nanoparticles of edaravone (EDR) have been found to be promising when injected into the nose [50].

Glioblastoma

Glioblastoma is the most serious of the brain tumors. Nanoparticles are used to deliver chemotherapeutics (doxorubicin, paclitaxel, temozolomide), siRNA and theranostic agents. Magnetic-Transferrin nanoparticles have been shown to be effective for glioma models [44].

Epilepsy

Epilepsy is a disease that impacts millions of people around the world. Anti-epileptic drugs are delivered in a sustained release manner with reduced side effects via the use of nanoparticles, as are neuroactive peptides and gene therapies.

Traumatic brain injury

TBI has a primary mechanical injury and secondary injury cascades. Nanoparticles carry the agents of neuroprotection, anti-inflammation and anti-oxidation.

Amyotrophic lateral sclerosis

In ALS, the motor neurons die. Nanoparticles are used to carry factors that are neuroprotective, siRNA that targets SOD1, and anti-inflammatory agents.

Table 3: Nanomedicine applications across neurological disorders.

Disease	Disease Overview	Conventional Therapy	Nanomedicine Strategy	Representative Nanocarriers	Key Findings	Clinical Stage	References
Alzheimer's Disease	Amyloid-β plaques, tau tangles, neuroinflammation, synaptic loss	Cholinesterase inhibitors, NMDA antagonists	Aβ aggregation inhibitors, anti-tau agents, anti-inflammatory drugs, neuroprotective factors, siRNA; enhanced BBB delivery	Liposomal vaccines (ACI-24, ACI-35.030); transferrin-conjugated PLGA NPs	Enhanced BBB penetration, reduced Aβ burden, improved cognitive function	Phase I/II	[31,46,47]
Parkinson's Disease	Dopaminergic neuron loss, α-synuclein aggregation (Lewy bodies), motor symptoms	L-DOPA, dopamine agonists, MAO-B inhibitors	Dopamine agonists, GDNF, α-synuclein aggregation inhibitors, anti-inflammatory agents	LY-03003 (microparticles); POZ-rotigotine (polymeric NPs); intranasal edaravone NPs	Sustained release, improved bioavailability, neuroprotection	Phase III	[34,48]

Multiple Sclerosis	Autoimmune inflammatory demyelination, axonal injury	Interferons, glatiramer acetate, monoclonal antibodies, glucocorticoids	Immunosuppressive agents, neuroprotective agents, antigen-specific immunomodulation, remyelination	Liposomal vaccines (Xemys, Myeloxen); GSH-promoters; PEGylated liposomal methylprednisolone	Targeted anti-inflammatory delivery, immune tolerance induction	Phase II	[49,50]
Stroke	Cerebral ischemia or hemorrhage, neuroinflammation, oxidative stress	tPA thrombolysis, mechanical thrombectomy; neuroprotective and anti-inflammatory agents	Thrombolytic agents, neuroprotective agents (edaravone, antioxidants), anti-inflammatory agents, angiogenic factors	Intranasal edaravone NPs; ROS-responsive nanogels	Enhanced brain bioavailability, reduced ischemic damage, improved neurological outcomes	Preclinical	[48,50]
Glioblastoma	Aggressive primary brain tumor, poor prognosis (12–15 months survival)	Surgery, radiation, temozolomide chemotherapy	Chemotherapeutics (doxorubicin, paclitaxel), siRNA, gene therapy, photothermal/photodynamic therapy, immunotherapy	Transferrin-conjugated magnetic silica PLGA NPs (DOX + PTX); SPION-based theranostic NPs	Enhanced BBB penetration, tumor targeting, MRI-guided therapy	Preclinical/Clinical	[44,46]
Epilepsy	Recurrent spontaneous seizures, neuronal hyperexcitability, drug resistance in ~30%	Antiepileptic drugs (AEDs), surgery, ketogenic diet	Sustained-release AEDs, neuroactive peptides, gene therapy, anti-inflammatory agents, seizure-triggered release	Liposomal CBD/THC formulations; stimulus-responsive nanogels	Reduced systemic side effects, improved seizure control	Preclinical	—
Traumatic Brain Injury (TBI)	Primary mechanical injury followed by secondary injury cascades involving neuroinflammation, oxidative stress, and excitotoxicity	Supportive care, symptom management	Neuroprotective agents, anti-inflammatory drugs, antioxidants, neurotrophic factors, diagnostic nanoparticles	Various polymeric NPs, biomimetic NPs, magnetic NPs	Mitigation of secondary injury, neuroprotection, imaging-guided therapy	Preclinical	[9,10]
Amyotrophic Lateral Sclerosis (ALS)	Progressive motor neuron degeneration, muscle weakness, respiratory failure	Riluzole, edaravone (modest survival benefit)	Neuroprotective agents, neurotrophic factors (GDNF, BDNF), siRNA targeting SOD1, autophagy enhancers, anti-inflammatory agents	PEGylated IGF-1; CNM-Au8 (gold nanocrystals); exosome-based delivery	Motor neuron protection, reduced protein aggregation	Phase II/III	[46]

TARGETED DRUG DELIVERY STRATEGIES

Ligand-Mediated Targeting

Specific recognition of BBB endothelium receptors or target cells can be achieved by using targeting ligands, such as antibodies, peptides or aptamers, which can be coated on nanoparticles. The molecules of ligands for TfR, LDLR and insulin receptor have been investigated to a large extent [19]. The artificial apolipoprotein coronas aid in the transport by the LDLR [46].

Receptor-Mediated Transport

The receptor-mediated transcytosis involves using natural transport vehicles. Ligands for TfR, LDLR and insulin receptor induce receptor internalization and vesicular transport. TfR has been a very interesting target for non-competitive epitope targets [16].

Cell-Penetrating Peptides (CPPs)

CPPs (TAT, penetratin, transportant) interact through electrostatic interactions to promote adsorptive-mediated transcytosis. CPPs have been attached to nanoparticles and liposomes and polymeric micelles [22].

Intranasal Delivery

Intranasal is a route of administration which takes advantage of the trigeminal and olfactory nerves to cross the BBB. Enhanced nasal residence time and permeation via nanoparticles. Intranasal administration of edaravone nanoparticles has shown to increase brain bioavailability [50].

Focused Ultrasound-Assisted Delivery

Localized delivery of drugs is achieved by disruption of BBB for a limited period of time with the use of focused ultrasound and microbubbles. To improve the accumulation in the brain, FUS has been paired with nanoparticles [20].

Stimulus-Responsive Nanoparticles

Stimulus-responsive nanoparticles are engineered to release payloads in response to a stimulus, such as a pH change or redox potential, temperature, enzymes, etc. Glutathione responsive nanoparticles are those that will release contents in a redox-sensitive way through disulfide bond [4].

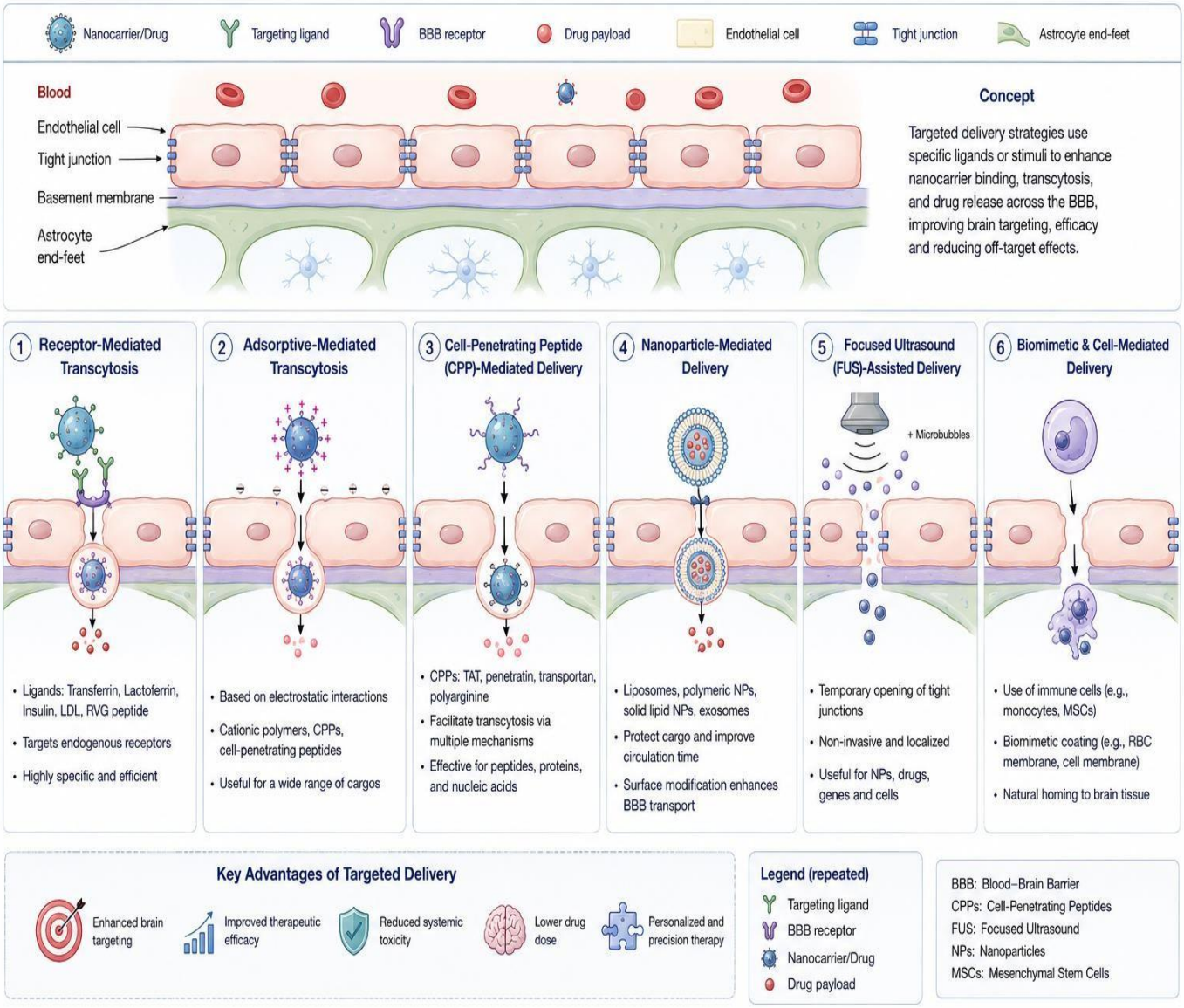


Figure 3: Targeted delivery strategies across the BBB.

NANOTHERANOSTICS AND PRECISION MEDICINE

Diagnostic Nanoparticles

Nanoparticles have both diagnostic and therapeutic properties for theranostic applications. The imaging modalities are MRI (iron oxide, gadolinium), CT (gold, iodine), PET (radionuclides) and optical imaging

(quantum dots, fluorophores) [23].

MRI Contrast Agents

Iron oxide nanoparticles (SPIONs) are used to enhance T2 MRI for tumor margin delineation, vascular permeability and nanoparticle biodistribution. Theranostic nanoparticles using spin saturated iron oxide nanoparticles (SPION) are nanoparticles that have both MRI contrast and hyperthermia or drug delivery.

Quantum Dots

Long-term cellular and molecular imaging of disease-specific proteins is possible with quantum dots. Adopting biocompatibility challenges, quantum dots with low toxicity and high biocompatibility have been developed [23].

Personalized Medicine and Companion Diagnostics:

Nanomedicine allows patient stratification, optimal therapeutic selection, real-time monitoring, and companion diagnostics. Personalized strategies are possible by using genomic, molecular and imaging data integrated together [6].

ARTIFICIAL INTELLIGENCE IN NANOMEDICINE

AI-Assisted Nanoparticle Design

AI/ML can be used to design nanoparticles rationally with optimized physicochemical properties without empirical optimization [5].

Machine Learning for Predictive Modeling

ML algorithms predict BBB permeability, protein corona formation, cellular uptake and cytotoxicity. The information is taken from the ever-expanding literature by using natural language processing [6].

Digital Twins Digital twin technology can be used to simulate the in silico behavior of nanoparticles and predict their biodistribution, clearance, and therapeutic effects. Digital twins help to select individual doses and treatments [4].

Network Pharmacology Integration Network pharmacology is a systems-level optimization approach for nanotherapeutic strategies by connecting the homeopathy interactions network with the disease biology [8].

CLINICAL TRANSLATION

Clinical Trials

There are a few nanomedicines being developed for CNS applications, such as liposomal vaccines (ACI-24, ACI-35.030), gold nanocrystals (CNM-Au8), and polymeric nanoparticles (LY-03003, POZ-rotigotine). But the rate of transition failure from Phase II to III is still high [5].

Regulatory Challenges

Regulatory pathways are complex, involving integration on the pharmaceutical quality, material safety and device performance. Some of the major hurdles are physicochemical characterization, nanotoxicity assessment, reproducible manufacturing, and demonstration of clinical benefit [4].

Manufacturing Challenges

Consistency of the production steps and quality attributes such as size distribution, drug loading, release kine-

tics, sterilization, stability, compatibility with administration device are essential for commercial scale manufacturing [6].

Commercialization

High development costs, regulatory complexity, competition with emerging therapies, and market access challenges pose a risk to commercialization. ALS, glioblastoma and progressive MS are the highest unmet medical needs [5].

Table 4: Selected Preclinical and Clinical Studies in Neurological Nanomedicine.

Nanomedicine	Formulation Type	Target Disease	Therapeutic Agent	Key Findings	Study Type	Stage	References
ACI-24	Liposomal vaccine	Alzheimer's disease	Aβ1-15 peptide	Reduced amyloid plaque burden, improved cognitive function; safe and immunogenic	Clinical	Phase II	[31]
ACI-35.03	Liposomal vaccine	Alzheimer's disease / Tauopathies	Phospho-tau peptide	Induced anti-tau antibody response; reduced tau pathology	Preclinical + Clinical	Phase I/II	[31]
LY-03003	Polymeric microparticles	Parkinson's disease	Rotigotine	Sustained release for 7 days; improved motor symptoms; reduced "on-off" fluctuations	Preclinical + Clinical	Phase III	[34]
POZ-rotigotine	Polymeric nanoparticles	Parkinson's disease	Rotigotine	Enhanced brain bioavailability; sustained dopamine receptor stimulation	Preclinical	Clinical	[34]
CNM-Au8	Gold nanocrystals	ALS	Catalytic gold nanocrystals	Enhanced mitochondrial function; improved energy metabolism; neuroprotection	Preclinical + Clinical	Phase II/III	[46]
Transferrin-PLGA NPs	Polymeric nanoparticles	Glioblastoma	Doxorubicin + Paclitaxel	Enhanced BBB penetration via TfR-mediated transcytosis; improved tumor targeting; increased survival in glioma models	Preclinical	Preclinical	[44, 46]
Magnetic silica PLGA NPs	Magnetic nanoparticles	Glioblastoma	Doxorubicin + Paclitaxel	MRI contrast enhancement; magnetic field-guided tumor targeting; improved therapeutic efficacy	Preclinical	Preclinical	[44]
GSH-PEGylated liposomal MP	Liposomes	Multiple sclerosis	Methylprednisolone	Targeted delivery to inflammatory lesions; reduced systemic side effects; improved clinical scores in EAE model	Preclinical	Preclinical	[50]
Xemys	Liposomal vaccine	Multiple sclerosis	Myelin peptide vaccine	Induced antigen-specific tolerance; reduced disease severity in EAE model	Preclinical	Phase II	[49]
Intranasal edaravone NPs	Polymeric nanoparticles	Stroke / Parkinson's disease	Edaravone	Enhanced brain bioavailability via intranasal route; neuroprotection against oxidative stress; improved neurological outcomes	Preclinical	Preclinical	[48]
PAMAM dendrimers	Dendrimers	Neuroinflammation	Anti-inflammatory agents	Enhanced accumulation in activated microglia;	Preclinical	Preclinical	[38]

				reduced neuroinflammation in neonatal brain injury models			
Exosome-liposome hybrids	Hybrid nanocarriers	Parkinson's disease	Neuroprotective agents	Synergistic neuroprotection; enhanced BBB crossing; improved therapeutic efficacy	Preclinical	Preclinical	[40]
Erythrocyte-mimetic NPs	Biomimetic nanoparticles	Various CNS disorders	Various therapeutics	Immune evasion; prolonged circulation; enhanced brain accumulation	Preclinical	Preclinical	[45]

TOXICOLOGICAL CONSIDERATIONS

Nanotoxicity

The toxicity of nanoparticles is caused by oxidative stress, mitochondrial dysfunction, lysosomal membrane permeabilization, ER stress and epigenetic modifications. The toxicities are related to size, shape, surface chemistry and crystallinity [27].

Immunogenicity

Nanoparticles induce complement activation, cytokine production, inflammation, and promote fast clearance by the RES, hypersensitivity, and chronic inflammation. It is possible that anti-PEG antibodies could be created on repeated use [4].

Biodistribution and Elimination

Nanoparticles are deposited in RES organs (liver, spleen and bone marrow). Accumulation in the brain is usually <1% of the administered dose. Elimination takes place via degradation, biliary/renal excretion and cell clearance. Inorganic nanoparticles can stay in the body [28].

Long-Term Safety

Cumulative toxicity, chronic inflammation, genotoxicity, immunogenicity, and effects of CNS microenvironment are concerns with chronic administration. Predictability is limited because of differences in handling of nanoparticles among species [27].

Ethical Considerations

Ethical considerations involve informed consent for novel approaches to treatment, equitable access, privacy considerations, research in vulnerable populations, and the implications of the ability to prolong life in debilitating circumstances [4].

FUTURE PERSPECTIVES

Smart Nanoparticles

Future nanoparticles will be equipped with multiple sensors, feedback-controlled drug delivery, closed-loop systems, and the integration of implants or wearable devices [6].

Biomimetic Systems

Perspective biomimetic nanoparticles will be developed into personalized membranes, hybrid systems, cell-free assembly and integration with the synthetic biology [45].

Gene-Editing Delivery

In neurological disorders, gene editing is being achieved using nanoparticles engineered to deliver CRISPR-Cas9 RNPs, mRNA encoding Cas9, guide RNAs and HDR templates [5].

RNA Therapeutics

siRNA, ASOs, microRNA modulators, and mRNA delivery are all being adapted for lipid nanoparticles for neurological applications [4].

Personalized Nanomedicine

Patient stratification, patient customized nanoparticle design, companion diagnostics, adaptive dosing, and monitoring circulating biomarkers are all features of personalized nanomedicine [6].

AI-Integrated Nanoplatforms

Closed-loop therapeutic systems that integrate diagnostic and therapeutic functions are made possible by the integration of AI.

CONCLUSION

Overall, nanomedicine could be a revolutionary method to the treatment of neurological diseases, and it has the ability to overcome the inherent shortcomings of traditional drug delivery, such as the blood–brain barrier. Nanomedicine allows the delivery of therapeutic agents to disease sites with unprecedented precision and efficiency by engineering nanocarriers with precisely controlled physicochemical properties, targeting capabilities and controlled release profiles. Nanocarrier platforms enable the development of a comprehensive toolbox to tackle the multifactorial nature of the pathophysiology of neurological diseases, ranging from liposomes to polymeric nanoparticles, lipid nanoparticles, and dendrimers, exosomes, and biomimetic systems. Disease-specific applications have shown that they can be used to improve therapeutic efficacy with less off-target toxicity. The new theranostic integration provides personalized treatment and the AI-enhanced design offers a time-saving advantage. The road to translation is still rough, though. The high failure rate in clinical development emphasizes the need for development of better preclinical models and understanding of biological interactions. The regulatory landscape needs to change, and manufacturing and commercialization approaches should take formulation complexity into consideration. However, the potential of nanomedicine to improve treatments for neurological diseases cannot be denied. The fusion of these technologies with the field of nanotechnology, molecular medicine and AI is unlocking new possibilities for precision therapeutics, which can be used to diagnose, monitor and treat neurological disorders in a minimally invasive and maximally effective way.

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