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Review Article

# Nanotechnology-Driven Strategies for Enhanced Brain Drug Delivery: A Review of Bio-Nanoparticle Systems

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**ABSTRACT**

The BBB is one of the biggest challenges in the treatment of neurological diseases, as it blocks more than 98% of drugs reaching the brain. In this review, current nanotech approaches to overcoming the BBB are compiled, including functionalized NPs (liposomes, polymeric NPs, SLNs, and inorganic NPs) with different modifications for targeting, including RMT, CPPs, positive charges, and non-invasive methods of administration such as intranasal delivery and MRgFUS. In parallel, biomimetic systems based on exosomes and cell membrane-coated NPs were reported. Examples are provided for the treatment of AD, PD, and GBM. Despite the impressive results at the preclinical stage, major challenges, including chronic toxicity, immunogenicity, manufacturing capacity, and regulatory issues, should be addressed before translation to clinical settings. The future of the brain-targeted delivery of drugs lies in the integration of personalized medicine, hybrid nanocarriers and real-time imaging.

**Keywords:** Blood-Brain Barrier (BBB), Brain-targeted Drug Delivery, Focused Ultrasound, Nanoparticles (NPs), Nanotechnology, Receptor-Mediated Transcytosis (RMT).

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## INTRODUCTION

The BBB is a unique, specialized and dynamically regulated interface that regulates homeostasis within the Central Nervous System (CNS) with cerebral endothelium cells, pericytes, and astrocytic end-feet intimately attached to each other (Wu *et al*., 2023). However, while such a unique composition of the BBB prevents entry of toxins and pathogens into the neuronal milieu, it inhibits the delivery of most drugs to the CNS that are being developed to treat neurological disorders. The effectiveness of these drug treatments is further hampered by active efflux transport systems, as well as rapid systemic clearance of drugs before they have the opportunity to reach their target site, due to strong tight junction formation (Teleanu *et al*., 2018). These limitations are applicable when treating diseases such as AD, PD, or GBM. It has been these problems, as well as the highly selective nature of transport systems across the BBB, that have been overcome by nanotechnology. Nanotechnology offers a paradigm-shifting way of formulating bio-nanoparticle systems where the size, surface chemistry, and surface coatings can be designed to either passively or actively cross the BBB (Lpez-Espinosa *et al*., 2024).

The Blood-Brain Barrier (BBB) is a selective and dynamic system consisting of brain endothelial cells, astrocytes, pericytes, and basement membrane, which collectively constitute the neurovascular unit. Tight Junction Proteins (TJPs) such as claudin-5, occludin, and Zonula Occludens-1 (ZO-1) play a crucial role in maintaining BBB integrity by regulating paracellular transport and shielding the brain from noxious agents.

Drug delivery via BBB can occur through passive diffusion, carrier-mediated transport, Receptor-Mediated Transcytosis (RMT), and Adsorptive-Mediated Transcytosis (AMT). Active efflux transporters such as P-glycoprotein (P-gp), Breast Cancer Resistance Protein (BCRP), and Multidrug Resistance-Associated Proteins (MRPs) play an important role in the efflux of xenobiotics and drugs, posing limitations to drug delivery to the brain. In diseases such as Alzheimer's disease, Parkinson's disease, and glioblastoma, the BBB becomes dysfunctional which poses opportunities for nanoparticle-based drug delivery.

This brief addition covers the topics requested by the reviewer on BBB physiology, TJPs, efflux transporters, RMT, AMT, and BBB dysfunction in diseases.

The focus of this review is to critically examine nanotechnology approaches that are being used to enable drug delivery to the brain. Topics to be discussed include nanoparticle architecture, surface engineering, techniques to non-invasively modulate

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the BBB, biomimetic nanocarriers, and the application to specific diseases. Limitations and future work are also discussed (Figure 1).

## METHODOLOGY

This article is presented as a narrative review. A comprehensive literature search was conducted using PubMed, Scopus, Web of Science, Google Scholar, ScienceDirect, and Embase. Publications from January 2015 to February 2026 were considered, while seminal studies published before this period were included when necessary to provide historical context. Search terms included combinations of blood-brain barrier, brain drug delivery, nanoparticles, liposomes, polymeric nanoparticles, solid lipid nanoparticles, exosomes, brain targeting, focused ultrasound, intranasal delivery, receptor-mediated transcytosis, and neurological disorders. Only peer-reviewed articles published in English were included. Conference abstracts, editorials, duplicate publications, and studies lacking sufficient scientific evidence were excluded. Approximately 235 publications were initially identified, of which 126 highly relevant studies were selected for critical

### Nanotechnology-Driven Strategies

#### *Nanoparticle Types*

Liposomes are lipid-bilayer vesicles which can encapsulate both hydrophilic and hydrophobic drugs and can be controlled for release and surface functionalization. Transferrin (Tf)-coated liposomes can be delivered to the BBB through receptor mediated transcytosis mechanism to the overexpressed Tf receptors of BBB endothelial and GBM cells. Brain delivery of doxorubicin carried by liposomes with transferrin coating is increased by 3-5 fold (Kawak *et al*., 2023). The release rate of liposomes is determined by the lipid composition of formulation. Saturated lipids (e.g. DSPC, HSPC) and cholesterol-based lipid bilayers prolonged release duration of about 10-18 days, while unsaturated lipids would deliver payload within 48 hr (Farzaneh *et al*., 2018).

PLGA polymeric NP is a biodegradable vehicle, approved by FDA and EMA, whose lactic-to-glycolic acid ratio dictates the rate of biodegradation and drug-release profile. For PD models, dopamine-loaded PLGA NPs can restore striatal dopamine to 40-60% levels and reverse behavioral deficits without any cardiovascular toxicity, which is better than the L-DOPA treatment (Pahuja *et al*., 2015). Albumin/PLGA hybrid NPs can increase motor coordination by over 100% in comparison with L-DOPA treatment (Monge-Fuentes *et al*., 2021).

SLNs encapsulate hydrophobic materials like curcumin into solid lipid matrices to prevent chemical degradation. Curcumin-loaded SLNs have shown significantly higher BBB penetration and higher AUC of curcumin in brain compared to free curcumin and significantly restored the cognitive functions of TgCRND8 transgenic mice (Sadegh *et al*., 2019).

Inorganic NPs, like AuNPs and IONPs are also useful for dual theranostic purposes. EGF-coupled AuNPs enable the targeted delivery of the nanocarrier to tumor cells, while IONPs can be employed for MRI tracking and guided by an external magnetic field can improve tumor accumulation to a great magnitude (Hu *et al*., 2023).

Choice of a proper nano-delivery system is based on the physicochemical characteristics of the drug, disease mechanism, and the chosen delivery approach. Liposomes and PLGA nanoparticles are the most researched systems owing to their high biocompatibility, flexibility, and good pharmacokinetics. Solid lipid nanoparticles show higher stability, yet they suffer from lower encapsulation efficiency in case of hydrophilic substances. On the other hand, inorganic nanoparticles possess special theranostic features as a result of imaging and drug delivery at the same time. Yet safety and possible toxicity issues prevent these nanoparticles from wide application. Biomimetic nanocarriers like exosomes and cell membrane-based nanoparticles exhibit better BBB penetration and targeting abilities. However, large-scale production, quality control, regulation issues, and affordability of the manufacturing process remain unresolved (Table 1).

### Surface Modifications

In RMT, native BBB transporter systems are utilized through linking NP with targeting ligands. Transferrin-linked NPs enable up to 10 times increased uptake of siRNA in the brain over non-targeted systems (Ahmed *et al*., 2021). Engineering bispecific antibodies with reduced TfR affinity unexpectedly enhance brain parenchyma entry as the antibodies dissociate from the brain endothelial TfRs at the blood-brain interface (Yu *et al*., 2011). Using acid-labile linkers between transferrin and NP core will improve the drug release from the endosome after transcytosis (Clark and Davis, 2015). CPPs like Angiopep-2 target low-density Lipoprotein Receptor-Related Protein 1(LRP1) of brain endothelial cells to realize RMT, while the positive charges of cationic CPPs (TAT, Penetratin, etc.) interact with the negatively charged cell membrane through electrostatic interactions. CPP functionalized NPs result in up to 5 times higher concentration of antiretroviral drugs in the brain (Parrasia *et al*., 2022). Rabies Virus Glycoprotein (RVG) functionalized NPs provide an approach for delivery in the cortex of neurodegenerative disease models (Pirhaghi *et al*., 2024). Adsorptive-Mediated Transcytosis (AMT) is a complementary strategy to RMT; positively charged CBSA NPs have significantly enhanced brain accumulation relative to neutral NPs. A combined strategy of positive surface charge coupled with receptor-targeting ligand provides both the desired specificity and the reduced generation of ROS, often associated with cationic systems (Hersh *et al*., 2022).

### BBB Disruption and Non-invasive Delivery

Focused Ultrasound (FUS) combined with intravenous microbubbles opens the BBB temporarily via acoustic cavitation. Clinical trials have proved that it is safe and feasible for recurrent GBM and intratumoral chemotherapy levels have been significantly enhanced using the SonoCloud device (Carpentier *et al*., 2016). With MR-guided FUS (MRgFUS), the BBB opening could be delivered more precisely. Progression-free survival is also increased in glioma patients under MRgFUS treatment (Idbaih *et al*., 2019). Potential inflammatory response to pulsed FUS still should be considered as a safety concern and examined for longer time (Kovacs *et al*., 2017).

Intranasal delivery directly bypasses the BBB using olfaction and trigeminal nerve from nasal mucosal to CNS. High bioavailability and patient compliance are achieved with CPP-drug conjugates and NP-based drugs via intranasal delivery (Figure 2) (Maeng and Lee, 2022).

### Biomimetic and Stimuli-Responsive Systems

The BBB can be navigated by endogenous vesicles-exosomes-via receptor-mediated endocytosis, or genetically engineered to deliver the CRISPR-Cas9 machinery with much lower immunogenicity and fewer off-target effects compared with viral vectors (Meneghini *et al*., 2021). Tailoring the surface ligands of exosomes also enhanced target specificity for GBM and AD (Xu *et al*., 2021). The first significant example showed that, after intravenous injection, exosomes carrying siRNA can deliver to specific neurons to silence targeted genes in mice (lvarez-Erviti *et al*., 2011). Cell membrane coated NPs-such as erythrocyte, leukocyte or cancer cell membrane coated NPs-take advantage of mimicking native biological surfaces to bypass the immune clearance and home in on inflammation or tumor tissues. By coupling with external stimuli-responsive systems (e.g., acidic pH ~5.5 in tumor microenvironment, enzymes, temperature or external stimuli such as magnetic fields or ultrasound), the release rate of drugs is triggered spatiotemporally in the tumor site and thus reduce the systemic toxicity of the drugs (Qiao *et al*., 2019).

## DISCUSSION

Nanotechnology represents a paradigm shift in the treatment of neurological disorders by providing multifunctional platforms for crossing, modulating, and utilizing the BBB. Engineered nanocarriers combined with surface bioconjugation and physical disruption methods directly tackle the historically dual limitations of poor CNS bioavailability and off-target distribution associated with conventional treatments.

Despite the translational potential, a convergence of limitations hinders the bench-to-bedside application of such systems. High-dose viral vectors and immunogenic nanocarrier components raise concerns regarding long-term toxicity, in particular, neurotoxicity, posing a major safety challenge. Large-scale manufacturability is a considerable bottleneck: producing monodispersed and highly pure nanoparticle formulations at clinical scale with reproducible characteristics requires sophisticated automated closed-system processes that carry high costs (Chang *et al*., 2022). Different approaches between the FDA and EMA toward regulating the systems also present regulatory challenges that necessitate harmonized efficacy and safety standards (Figure 3).

Biological complexities also pose considerable translational challenges due to the inherent heterogeneity of the BBB. The variation in transporter expression (e.g., transferrin receptor) between regions, between individuals and during different diseases limit the applicability of rodent model studies, suggesting the necessity of humanized or organoid-based preclinical systems. Individual differences in BBB integrity, especially in the case of GBM, where compromised integrity is a feature of

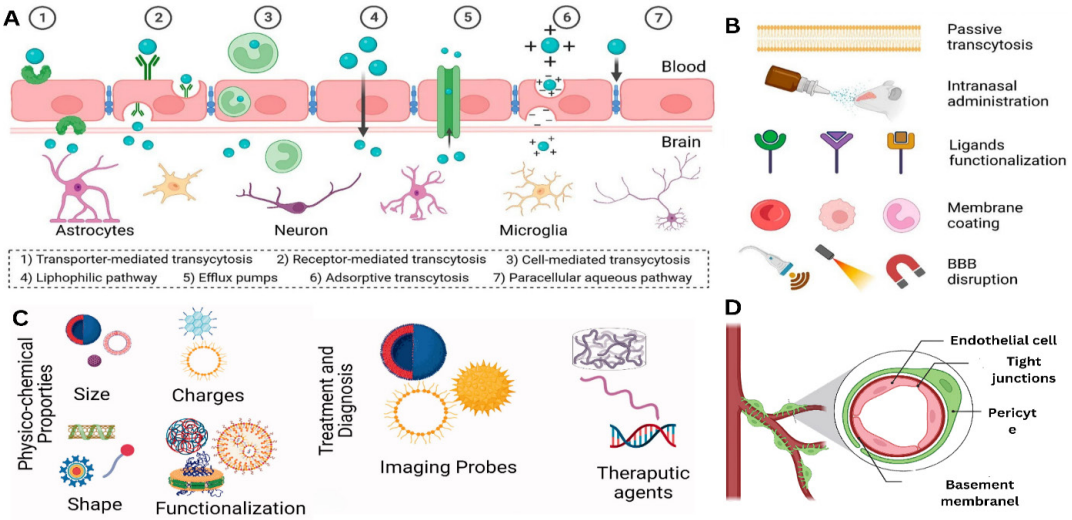


**Figure 1:** Structure and mechanisms for crossing and drug delivery A) Schematic diagram of different mechanisms for BBB crossing. B) Engineered materials for brain-targeted drug delivery C) Factors affecting the transport of substances between the BBB and tumor cells D) Schematic diagram of the BBB structure.

the disease and a therapeutic opportunity, call for personalized delivery approaches.

Biomimetic delivery strategies with exosomes or cell membrane-coated nanoparticles hold promise in alleviating the immune challenges and concerns for immunogenicity, although their long-term safety profile and interaction mechanisms with the immune system require further investigation. Integrating CRISPR-Cas9 delivery with nanocarriers opens a new realm for gene therapy in neurodegenerative disorders, although further work on off-target effects and overall CNS delivery efficiency needs to be addressed.

One of the major hurdles in using nanoparticle-mediated drug delivery is their long-term safety. Though biodegradable carriers like liposomes and PLGA nanoparticles offer good biocompatibility properties, long-term administration may cause immune reactions, inflammation, and unwanted distribution into other organs such as the liver and spleen. Biodegradability, biodistribution, and elimination should therefore be evaluated carefully to avoid systemic toxicity.

On the other hand, inorganic nanoparticles such as gold and iron oxide nanoparticles have been found to have exciting potential in theranostics, although there are still questions about long-term bioaccumulation, oxidative damage, neurotoxicity, and limited biodegradation. Future work in this area should concentrate on developing safety criteria and toxicology analysis, and optimizing nanoparticle composition to ensure biocompatibility without reducing their efficiency.

Future studies must focus on creating truly multifunctional and stimulus-responsive nanocarriers capable of targeting, controlled release and real-time imaging. Highly individualized therapy utilizing personalized medicine-like nanoparticle design based on patient biomarkers and disease stage holds great promise to improve treatment precision. Collaboration between nanotechnologists, clinicians, ethics bodies, and regulators is crucial to the success of this endeavor in overcoming the challenges

**Table 1: Comparative summary of nanoparticle systems for brain drug delivery.**

| Nanoparticle System | BBB Penetration Mechanism | Drug Loading Capacity | Pharmacokinetic Characteristics | Major Advantages | Major Limitations | Clinical Translation Potential |
|---|---|---|---|---|---|---|
| Liposomes | Primarily receptor-mediated transcytosis (RMT) following ligand functionalization (e.g., transferrin, lactoferrin). | High (hydrophilic and lipophilic drugs). | Prolonged circulation, improved bioavailability, reduced systemic toxicity. | Excellent biocompatibility, surface modification flexibility, controlled drug release. | Drug leakage, physical instability, rapid clearance without PEGylation. | High; several liposomal formulations are clinically approved for other indications, supporting future brain-targeted applications. |
| Polymeric Nanoparticles (PLGA) | Endocytosis and ligand-mediated transport. | Moderate to High | Sustained and controlled drug release with tunable degradation. | Biodegradable, FDA-approved polymer, excellent stability, controlled release. | Initial burst release, relatively complex manufacturing. | High; widely investigated in preclinical and translational research. |
| Solid Lipid Nanoparticles (SLNs) | Adsorptive-Mediated Transcytosis (AMT) and endocytosis. | Moderate | Improved drug stability and prolonged circulation. | High physical stability, low toxicity, protection of labile drugs. | Limited loading of hydrophilic drugs, possible drug expulsion during storage. | Moderate to High; promising for neurodegenerative disorders. |
| Inorganic Nanoparticles (Gold, Iron Oxide) | Passive diffusion, receptor-mediated transport, or magnetic targeting. | Moderate | Long circulation with imaging capability. | Theranostic applications, MRI compatibility, magnetic guidance. | Potential long-term accumulation, oxidative stress, neurotoxicity concerns. | Moderate; requires extensive safety evaluation before routine clinical use. |
| Exosomes | Natural receptor-mediated endocytosis and membrane fusion. | Moderate | Excellent stability and prolonged biological circulation. | High biocompatibility, immune evasion, efficient BBB crossing. | Difficult isolation, purification, standardization, and scale-up. | Very High; considered one of the most promising next-generation delivery platforms. |
| Cell Membrane-Coated Nanoparticles | Biomimetic membrane recognition and receptor-mediated interactions. | Moderate | Extended circulation with reduced immune clearance. | Excellent targeting specificity, prolonged half-life, immune camouflage. | Complex fabrication, reproducibility, manufacturing challenges. | Emerging; promising but requires further clinical validation. |

**Table 2:** **Nanotechnology applications in selected neurological disorders.**

| Disorder | NP System | Mechanism | Key Outcome |
|---|---|---|---|
| Alzheimer's disease | PLGA NPs (KLVFF-conjugated) | Aβ fibril disruption | Reduced Aβ aggregation; cognitive improvement in preclinical models |
| Alzheimer's disease | Exosomes (siRNA-loaded) | BACE1 silencing via RNAi | Suppressed Aβ production; reduced neuroinflammation *in vivo* |
| Parkinson's disease | Albumin/PLGA NPs | Dopamine BBB delivery | >100% motor recovery vs. L-DOPA; sustained striatal dopamine |
| Glioblastoma | Liposomal doxorubicin (Tf-coated) | Receptor-mediated transcytosis | 3-5× higher brain drug uptake; improved preclinical survival |

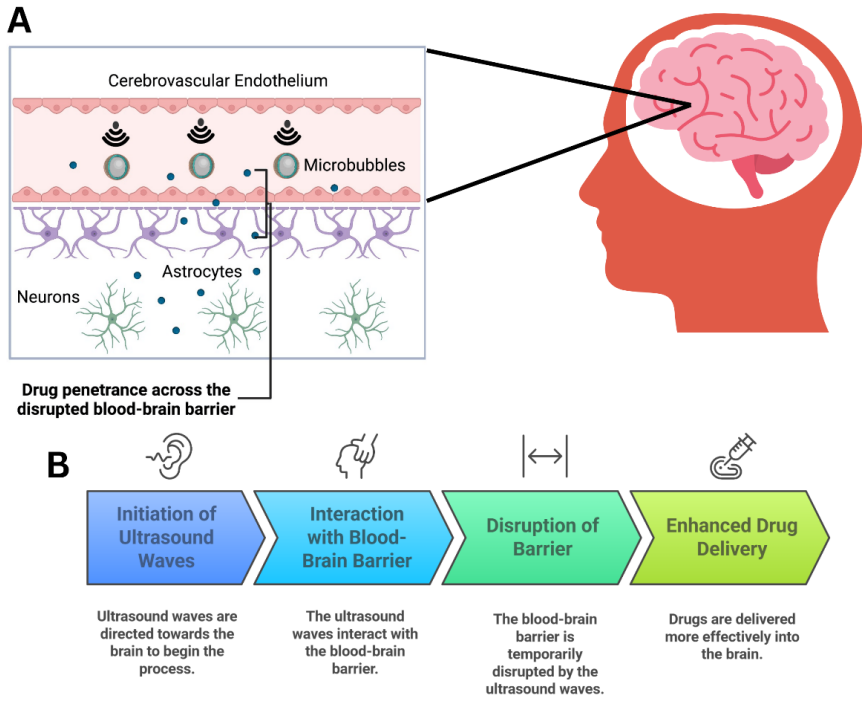


**Figure 2:** Ultrasound-mediated disruption of the Blood-Brain Barrier (BBB) enhances drug delivery to the brain. (A) Key components of the cerebrovascular endothelium, including microbubbles, astrocytes, and neurons, are involved in BBB modulation. Licensee MDPI, Basel, Switzerland. (B) Process of ultrasound wave application and interaction with the BBB, leading to temporary disruption and improved drug penetration into brain tissue.

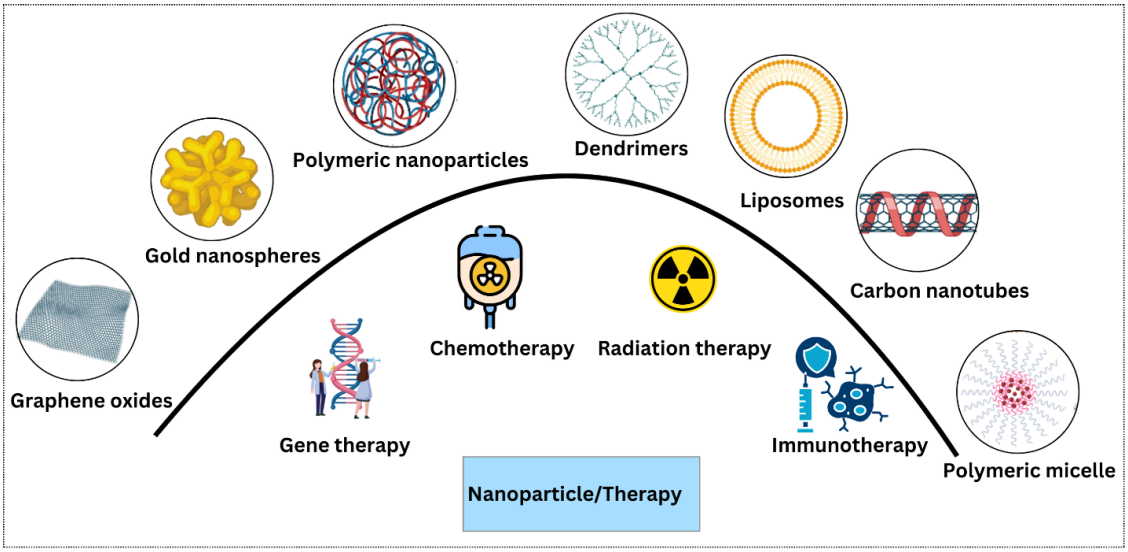


**Figure 3:** Nanocarriers and types of therapy currently used to target GBM.

inherent to bridging the bench-to-bedside gap responsibly and effectively before widespread clinical applications.

There are various scientific, manufacturing, and regulatory hurdles that must be overcome to enable the clinical translation of the brain drug delivery system through nanoparticles. Despite the success in gaining FDA/European Medicines Agency (EMA) approvals for some nanomedicines, such as Doxil® (doxorubicin), AmBisome® (amphotericin B) and Onpattro® (patisiran), for non-CNS diseases, there have been few nanoparticle formulations that have reached the clinic for CNS diseases.

Besides the challenge related to the BBB itself, the individual differences of patients and the requirement for prolonged safety testing have hindered the clinical use of the nanoparticles. Furthermore, large-scale manufacturing needs precise synthesis, stringent quality control, and compliance with Good Manufacturing Practice (GMP). The regulatory agency, such as FDA/EMA, will need extensive assessment of pharmacokinetic, biodistribution, toxicity, and efficacy prior to approval. Moreover, high cost of production, scalability, and regulatory challenges represent major hurdles for commercialization.

## CONCLUSION

Nanotechnology-empowered bio-nanoparticle systems have already made great progress in brain-targeted drug delivery by providing flexible, engineerable platforms which can either circumvent or exploit the BBB. Liposomes, polymer NPs, SLN and inorganic NP, further enhanced by surface modification and non-invasive administration approaches, showed promising efficacy in preclinical studies in the three main diseases of AD, PD and GBM (Table 2). Biomimetic methods based on exosomes or cell membrane coating bring with them advantages of biocompatibility and immune evasion. A thorough validation of nanomedicines for clinical application is necessary by eliminating the issues in the toxicity, scale-up, harmonization of regulation and inter-patient variability through effective multi-disciplinary collaboration and standardized evaluation method.

## ABBREVIATIONS

**AD:** Alzheimer's disease; **AMT:** Adsorptive-mediated transcytosis; **AuNPs:** Gold nanoparticles; **BBB:** Blood-brain barrier; **CNS:** Central nervous system; **CPPs:** Cell-penetrating peptides; **CRISPR:** Clustered regularly interspaced short palindromic repeats; **EGFR:** epidermal growth factor receptor; **EMA:** European Medicines Agency; **FUS:** Focused ultrasound; **GBM:** Glioblastoma multiforme; **HPLC:** High-performance liquid chromatography; **IONPs:** Iron oxide nanoparticles; **LRP1:** Low-density lipoprotein receptor-related protein 1; **MRgFUS:** Magnetic resonance-guided focused ultrasound; **MRI:** Magnetic resonance imaging; **NPs:** Nanoparticles; **PD:** Parkinson's disease; **PLGA:** Poly(lactic-co-glycolic acid); **RMT:** Receptor-mediated transcytosis; **ROS:** Reactive oxygen species; **RVG:** Rabies virus glycoprotein; **SLNs:** Solid lipid nanoparticles; **Tf:** Transferrin; **TfR:** Transferrin receptor; **TMZ:** Temozolomide.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHORS CONTRIBUTIONS

**Suraj Kumar:** Conceptualization, Literature Search, Manuscript Drafting, Revision. **Pranita Jirvankar:** Conceptualization, Critical Review, Final Approval of Manuscript.

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