

# How Precise are Nanomedicines in Overcoming the Blood–Brain Barrier? A Comprehensive Review of the Literature

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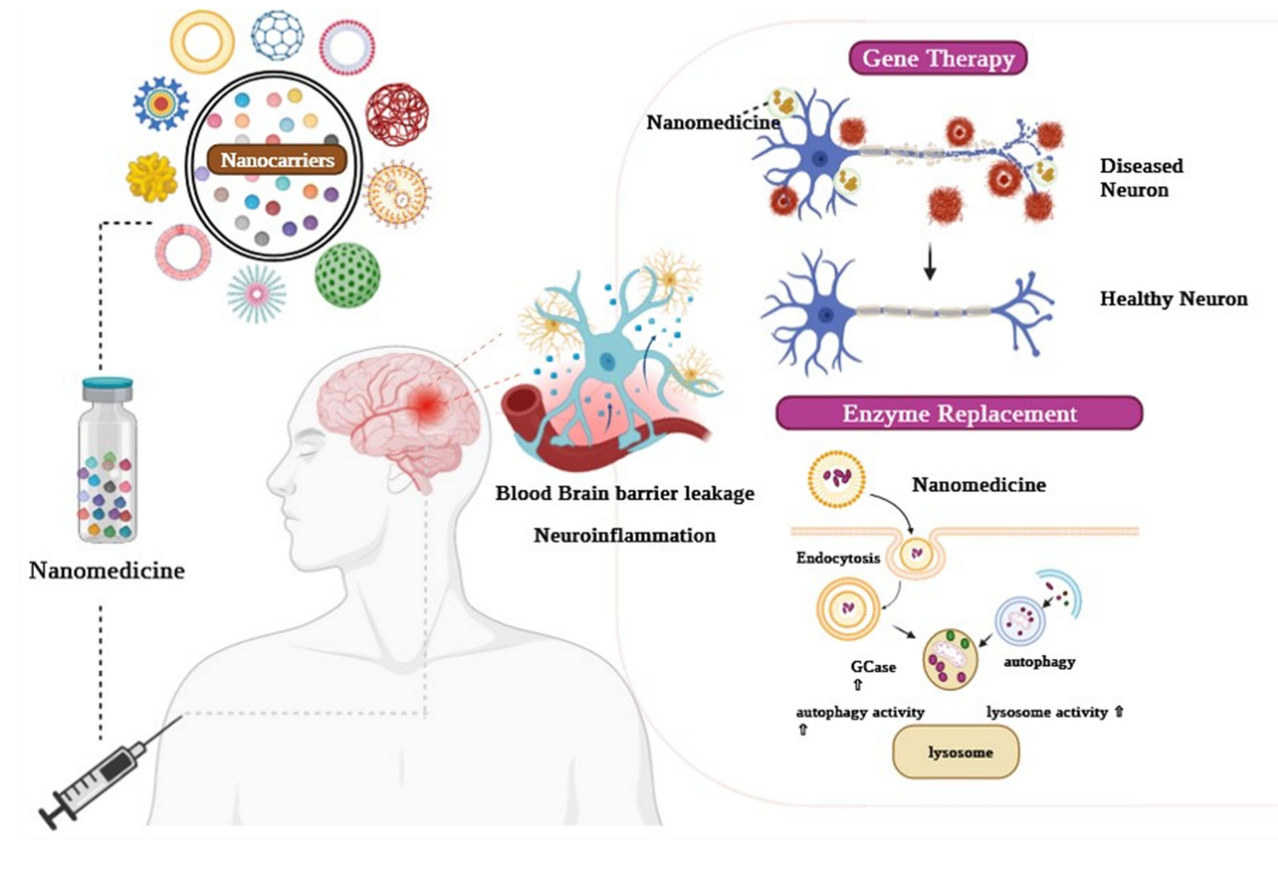
**Abstract:** New nanotechnology strategies for enhancing drug delivery in brain disorders have recently received increasing attention from drug designers. The treatment of neurological conditions, including brain tumors, stroke, Parkinson's Disease (PD), and Alzheimer's disease (AD), may be greatly influenced by nanotechnology. Numerous studies on neurodegeneration have demonstrated the effective application of nanomaterials in the treatment of brain illnesses. Nanocarriers (NCs) have made it easier to deliver drugs precisely to where they are needed. Thus, the most effective use of nanomaterials is in the treatment of various brain diseases, as this amplifies the overall impact of medication and emphasizes the significance of nanotherapeutics through gene therapy, enzyme replacement therapy, and blood-barrier mechanisms. Recent advances in nanotechnology have led to the development of multi-functional nanotherapeutic agents, a promising treatment for brain disorders. This novel method reduces the side effects and improves treatment outcomes. This review critically assesses efficient nano-based systems in light of obstacles and outstanding achievements. Nanocarriers that transfer medications across the blood-brain barrier and nano-assisted therapies, including nano-immunotherapy, nano-gene therapy, nano enzyme replacement therapy, scaffolds, and 3D to 6D printing, have been widely explored for the treatment of brain disorders. This study aimed to evaluate existing literature regarding the use of nanotechnology in the development of drug delivery systems that can penetrate the blood-brain barrier (BBB) and deliver therapeutic agents to treat various brain disorders.

**Keywords:** drug delivery, nanomedicine, nano-therapeutics, nanocarriers, blood-brain barrier

## Introduction

The incidence and prevalence of central nervous system (CNS) illnesses are progressively rising, posing serious threats to human life, and increasing socioeconomic expenses associated with providing medicinal treatment.<sup>1</sup> The number of disability-adjusted life-years (DALYs), a crucial indicator of the burden of neurological diseases, is rising.<sup>2</sup> In India, the incidence of neurological disorders is growing alarmingly—stroke (37.9%), headache disorders (17.5%), epilepsy (11.3%), cerebral palsy (5.7%), and encephalitis (5.3%).<sup>3</sup> The two categories of CNS diseases that affect the brain's neurological functions are acute brain injury and neurodegenerative disorders. The most common brain injuries are stroke, cerebral ischemia, and epilepsy, whereas chronic injuries include Alzheimer's Disease (AD), Parkinson's Disease (PD), and Huntington's disease.<sup>4</sup> Neurological disorders involve the progressive deterioration of neuronal structure and function, often leading to neural death.<sup>5</sup> These disorders affect the central and peripheral nervous systems, including the brain, spinal cord, cranial and peripheral nerves, nerve roots, autonomic nervous system (ANS), neuromuscular junctions, and muscles. These disorders include cerebrovascular diseases, PD, AD, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, brain tumors, stroke, neuroinfections, autism spectrum disorders, and schizophrenia.<sup>6,7</sup> The presence of peripheral and blood–brain barriers (BBB) makes it more challenging to deliver drug molecules to target sites in the CNS.<sup>8</sup> The most delicate and intricate organs in the human brain are shielded by the BBB. It protects

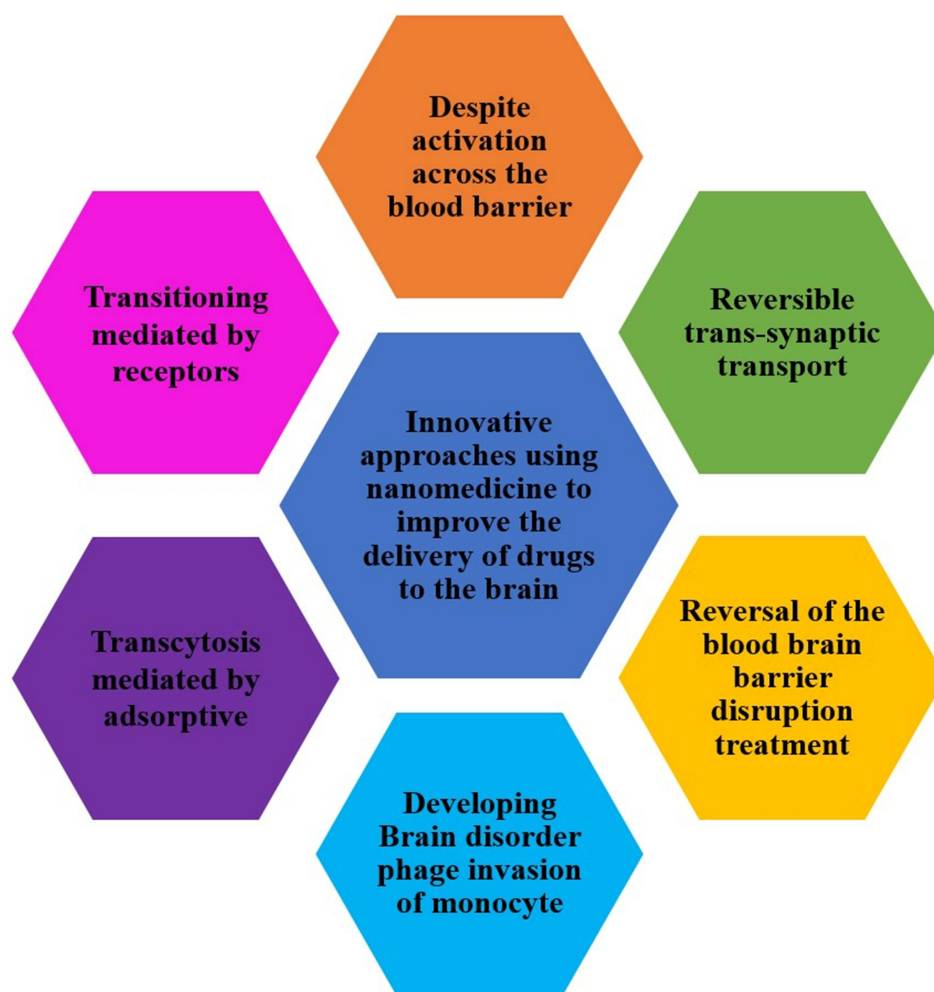
## Graphical Abstract



brain neurons against destructive and poisonous substances in the blood and disturbs drug penetration into brain tissues.<sup>9</sup> The brain is differentiated from the other parts of the body by strong barriers that prevent the transfer of drug molecules to the CNS. These limitations necessitate the development of new therapeutic approaches to treat brain diseases. Figure 1 introduces innovative nanoparticle (NP)-based brain medication delivery methods.<sup>10</sup>

Recently, nanotechnology has played a vital role in numerous disease states and has had more therapeutic success. Studies have shown that nanotechnology is more effective than current therapeutics (Figure 1). Some of the nanotechnology applications include acting as (NCs) for drug delivery systems,<sup>11</sup> nano-based therapeutic approaches, nano-based stem cell therapy, nano gene therapy,<sup>12</sup> nano enzyme replacement therapy, and personalized nanomedicine for future therapeutics. Gene therapy has a significant impact on the neurological sciences. It suppresses or replaces the abnormal cells in their genetic elements and acts as a nano gene carrier in several neurological disorders. Owing to the BBB in patients with glioblastoma, traditional intracerebral injections can result in neurological damage and poor transgene signatures. To address these challenges, studies have explored the application of gene therapy by designing non-viral gene delivery systems for treating angiogenesis for effective gene therapy without damaging brain tissues.<sup>13</sup>

To bolster these endeavors, the incorporation of nano-based gene therapy has emerged as a promising approach for treating various cancerous cell types. Enzyme replacement therapy (ERT) is a promising treatment option. It replaces or supplements enzymes in patients with enzyme deficiencies or malnutrition. The enzyme was encapsulated in biocompatible nanosubstances, including micelles, liposomes, polymers, and lipid-based NPs. Figure 2 briefly overviews the ideal NCs qualities for delivering drugs to the brain.<sup>1</sup> With the help of a NC, we can overcome the drawbacks of ERT, including immunological response and degradation,<sup>14</sup> and preserve enzyme functions and activity (Figure 2). This is an effective pharmacological response that controls the release.<sup>15–19</sup> NCs are precise and accurate in drug release, exactly targeting drug delivery to the brain. The characteristic of



**Figure 1** Represents the dynamic landscape of nanomedicine, providing a detailed insight into the multifaceted strategies propelling advances in brain drug delivery and describing the design of novel NP-based techniques and tactics aimed at delivering drugs to the brain.

NCs involves, biocompatibility with diverse substances, protecting the brain cells non-invasively, stability in the bloodstream, the capacity of a molecule to pass through vessels, an extended time for blood circulation, safe, and decomposable.<sup>17–19</sup>

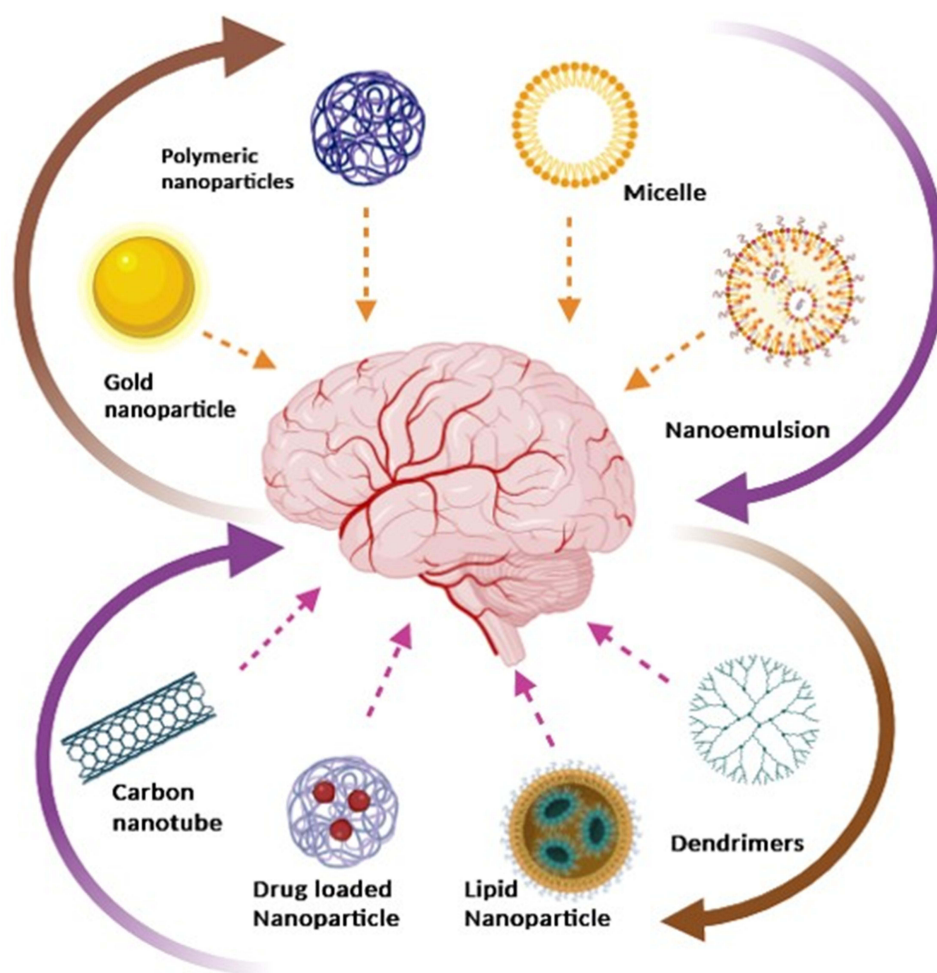
Additionally, targeting molecules such as antibodies, peptides, and aptamers were loaded with NCs that penetrate the BBB and blood-ocular barriers and directly reached the target sites. This review aims to highlight new findings in the development of nano-based gene therapy and nano-based enzyme replacement therapies for their potential use in the treatment of neurological diseases, especially brain tumors and other neurodegenerative disorders, as well as ongoing clinical trials and other therapeutic challenges in the development of nano-based therapeutic solutions from bench to bedside for overcoming neurodegenerative diseases.

## How Critical are Neurological Disorders and Their Treatment?

Neurological illnesses are the biggest threat to the healthcare system, especially in older people. They suffer from neurological issues such as neuroinflammation, neurodegeneration, and cognitive dysfunction. Treatment strategies are often palliative and inadequate to address the disorders.<sup>20</sup> The most prevalent neurological disorders are AD, PD, stroke, and brain cancer, which are the most challenging conditions for designing potent therapeutics.

## Alzheimer's Disease

The most common form of dementia is AD, which affects nearly 50 million individuals were affected globally.<sup>21,22</sup> Cognitive deficiencies are treated through the intranasal delivery of medicines that target neurotransmitters or enzyme regulations.<sup>23</sup> The



**Figure 2** Diverse nano-based therapies for advancing brain disorder treatment.

Food and Drug Administration (FDA) has only permitted four therapies for AD, and the targets focus on various elements of the two primary molecular processes involved in their accumulation of A $\beta$  peptide and neurofibrillary tangles (NFT) of p-tau protein.<sup>24</sup> However, these drugs show a significant increase in therapeutic failure due to their inability to penetrate the membranes of neuronal cells, instability, neurotoxicity, and other pharmacokinetic and pharmacodynamic properties.<sup>22</sup> To overcome this problem, NPs, such as lipids, polymers, and metals, act as drug delivery systems and even diagnose diseases. These NPs act as drug delivery systems to effectively treat chronic CNS disorders. It is difficult for these drugs to reach organs such as the CNS, especially the BBB region, which must penetrate and regulate the release of drugs.<sup>25</sup>

## Parkinson's Disease

PD is the second most common neurological degenerative disorder that worsens over time and causes tremors, muscular rigidity, uneven gait, and issues with balance and coordination. Hereditary and nongenetic factors trigger PD, and age is considered the primary factor.<sup>26,27</sup> Numerous processes are crucial in developing PD, including the misfold and aggregated  $\alpha$ -synuclein, mitochondrial dysfunction, dysfunction of protein clearance mechanisms, ubiquitination of proteasome region, and autophagy of lysozyme and neurological inflammation.<sup>27</sup> Similarly, Lewy bodies act as the development of abnormal proteins such as  $\alpha$ -synuclein in the neuronal cell bodies affected and featured in PD.<sup>28</sup> Owing to BBB restrictions, current drug delivery to the brain cannot restore or maintain the cytoarchitecture acceptably.<sup>29</sup> Numerous nanodelivery systems, such as nano-phytobioactive substances, have shown promise in PD treatment. The use



of solid lipid NPs, nanolipid carriers, and nanoliposomes has further enhanced the permeability, solubility, and stability of substances for delivery to the target region.<sup>30</sup>

## Stroke

Stroke is a fatal and severely disabling brain condition. Most cases of stroke are ischemic. Currently, no effective treatments are available in the clinic, partly because it is difficult to deliver medications to ischemic areas in the brain.<sup>31</sup> It is characterized by the hemorrhage or obstruction of cerebral blood vessels due to a lack of blood flow in the brain, leading to neurological impairment, oxidative stress, and brain cell malfunction.<sup>32</sup> A series of degenerative processes is initiated by cerebral ischemia, leading to the eventual loss of neurons. Reperfusion is a therapeutic technique used to treat ischemic stroke and involves the infusion of tissue plasminogen activator (t-PA) or mechanical thrombectomy (MT).<sup>33</sup> To overcome this problem, numerous neuroprotectants have been developed to reduce reperfusion-induced damage. However, all of them lack clinical approval because drugs cannot be effectively delivered to the brain through the BBB, drugs that circulate quickly, are unstable or poisonous, and it is difficult to select the proper drug regimen and dosages because of heterogeneity.<sup>31</sup> Drug-loaded liposome-based NC systems, polymeric and artificial carriers, and inorganic NPs are formulations that are effective against ischemic stroke.

## Brain Cancer

Brain cancer is the most fatal and invasive CNS disease worldwide. It is associated with various primary and metastatic CNS malignancies. Brain cancer is considered alarming, and its high recurrence rates and frequent resistance to therapy are painful signs of neurological degradation, resulting in lower survival rates.<sup>12</sup> Glioblastoma multiforme (GBM), also known as grade IV malignant glioma, is an extremely invasive and aggressive tumor.<sup>34</sup> Current treatment options for GBM include surgical resection, chemotherapy, and radiation. Owing to the ineffective therapeutic choices for GBM, developing new methods and enhancing existing technology is crucial. Understanding the interactions between immune cells and malignant glioma cells, as well as the immunosuppressive properties of the tumor, is essential for a better understanding of the present difficulties. This interaction is governed by many variables that may be categorized as influencing factors for the BBB, immunosuppressive microenvironment, heterogeneity, subtype-specific glioblastoma genetic signatures, and irrelevant elements involved in modifying the impact of prior systemic therapy.<sup>35</sup> Liposome NC and drug substances conjugated with inorganic NPs, such as dendrimer-loaded NPs are ideal nanomedicine materials for GBM therapy.<sup>1</sup>

## How Advanced is Nanotechnology in Treating Brain Disorders?

Nanotechnology aims to design, create, and utilize nanomaterials with at least one dimension between 1 and 100 nm is the goal of nanotechnology.<sup>36</sup> Superparamagnetic and surface plasmon resonances are two examples of bulk-independent phenomena typically present at this size and are of interest to the medical community.<sup>22</sup> Interaction of proteins and nucleic acids with biomolecules and cells. They are similar in size to nanomaterials, particularly NPs.<sup>37</sup> A high surface-to-volume ratio of the nanometric size enhances biological recognition. This improves the sensing, making detection more efficient and accurate. Recently, the use of nanomaterials in precision medicine has also increased<sup>38</sup> (Figure 2 and Table 1).

## Nanocarrier for Drug Delivery

A pharmaceutical technique that has been developed to overcome these challenges uses virus-free NCs to deliver genetic treatments for brain disorders.<sup>48</sup> Inorganic NPs, including gold and iron oxide NPs, polymer-based NPs, micro/nanoemulsions, scaffolds, drug-loaded nanoemulsions, dendrimers, and carbon nanotubes, have been proposed and studied as NCs (Figure 2 and Table 1).<sup>1,49</sup> Nanomedicine-based gene delivery methods have several advantages over viral vectors, including improved targeting specificity, longer blood circulation, high loading capacity, manageable drug release, and decreased immunogenicity.<sup>50</sup> The sole treatment for brain disorders is symptomatic relief because the medication cannot overcome the BBB.<sup>51</sup> Nanotechnology-based therapy can overcome this limitation because of its advantages.<sup>52</sup> Several different types of NCs have received approval from the FDA to be used with commercially available drugs.

**Table I** Current State of Nanomedicine in Treating Different Brain Disorders

S. No	Drug Name	Nanocarrier	Disease	Route of Administration	Benefits and Outcomes	FDA Approved Status	References
1	CNM-Au8	Gold nanocrystals	Parkinson's disease	Oral	It has shown promise in enhancing brain function and reducing illness symptoms.	Phase II	[39]
2	Ferumoxytol	Iron oxide NPs	Brain neoplasms	Intravenous	It can provide targeted medication delivery and improved imaging to treat these cancers.	Phase II	[40]
3	L-DOPA	PLGA	Parkinson's disease	Intranasal	It shows potential for extending medication release and improving therapeutic effectiveness in treating the illness.	Nil	[41]
4	Cornell Dots	PEG-coated fluorescent silica nanoparticles	Malignant brain tumor imaging	Intravenous	It demonstrates the potential for sensitive and accurate tumor imaging to support diagnosis and therapy planning.	Phase I	[42]
5	AGulX	Gadolinium-based NPs made of polysiloxanes	Brain metastases	Intravenous	It holds out hope for improved imaging, enabling precise identification and characterization of brain metastases.	Phase II	[43]
6	Lomustine	Liposomes/Microcapsules	Brain tumor	Orally	These treatments provide the potential for enhanced drug distribution, greater therapeutic effectiveness, and lower systemic toxicity.	2010	[44]
7	APH-1105	Inhalation of Nanoparticles	Mild to moderate Alzheimer's disease	Intranasal	It demonstrates promise for increased medication delivery to the brain, which might result in better therapeutic effects.	Phase II	[45]
8	Nanotherm® (MagForce)	Inorganic and metallic nanoparticles	Glioblastoma multiforme	Intravenous injection	It shows promise for localized tumor eradication and tailored heat treatment.	2010	[1]
9	D-Penicillamine	(MPB-PE) and (PDP-PE) couples	Alzheimer's disease	Nasal Delivery	It has the potential to lead to more effective drug delivery and more focused treatment plans to slow the spread of illness.	2005	[46]
10	Rivastigmine	Poly(n-butyl cyanoacrylate)	Alzheimer's disease	Intravenous	It promises increased medication delivery to the brain, which might result in better cognitive performance and illness management.	2000	[47]
11	Nano-thermotherapy	Radiotherapy with decreased dosage and the use of magnetic iron-oxide nanoparticles	Glioblastoma multiforme	Intrathecal	It can increase radiation's effectiveness and boost patient outcomes for localized tumor heat treatment.	Phase II clinical trials	[1]

## Liposome

Spherical liposomes include a phospholipid bilayer and a water-soluble 100–400 nm core. By increasing lipophilicity, this bilayer helps macromolecules cross the blood-brain barrier.<sup>53</sup> Liposomal NPs offer several therapeutic advantages. NPs are commercially available and are easily accessible to researchers and clinicians. Additionally, the synthesis and encapsulation of therapeutic compounds within liposomal NPs is relatively simple, allowing for efficient production. One notable advantage of liposomal NPs is their enhanced solubility as therapeutic agents. Passive diffusion can be initiated once the liposomes enter the brain. Passive efflux initiates this process.<sup>54</sup> Apolipoprotein E (ApoE2) is delivered to the AD-damaged brain using a liposome carrier system modified with a mannose ligand and cell-penetrating peptides. The results showed that functionalized liposomes could safely and effectively transfer high gene concentrations to target tissues to treat AD.<sup>55</sup>

## Polymeric Nanoparticles

The polymeric NPs had a size range of 1–100 nm. Coupling of therapeutically active compounds to enable targeted drug administration for the treatment of brain gliomas has been extensively investigated in research studies.<sup>56</sup> Intratumoral delivery of anticancer drugs using NPs can treat malignant brain gliomas, such as glioblastoma multiforme.<sup>57</sup> In animals with GBM, Convection-enhanced delivery (CED) and NP encapsulation improved drug penetration, distribution, and survival.<sup>58</sup> The intravenous injection of Dox into poly(butyl cyanoacrylate) NPs led to increased drug accumulation at glioma rat tumor site.<sup>59</sup> The most innovative method of drug delivery, particularly for NDs, is the use of polymeric NPs. These block-copolymeric compounds are easily eliminated without posing a systemic toxicity risk because they comprise monomers.<sup>60</sup> These polymers are ideal for NP synthesis because of their biocompatibility and biodegradability.<sup>61</sup> Recent research has focused on using curcumin-loaded PLGA NPs to improve drug delivery and reduce inflammation and oxidative stress in the treatment of AD.<sup>62</sup> Polymeric biodegradable NPs functionalized with an antibody and polyethylene glycol (and) in transgenic AD mice.<sup>63</sup> Exposure to PEGylated NPs can improve memory impairment and considerably reduce A-soluble peptide levels.<sup>64</sup>

## Dendrimers

Dendrimers, which are nanosized and highly specific formulations, may cure neurodegenerative diseases.<sup>65</sup> The size, core-shell composition, and surface functional groups of dendrimers can be altered to construct brain-delivered medication and gene NCs.<sup>66</sup> The anti-amyloidogenic properties of the dendrimers may help treat prions, PD, and AD. Owing to their properties, dendrimers are medical equipment that sterilize solutions. Phosphorus-containing dendrimers have also been explored for the prevention of prion infection prevention.<sup>67</sup> Misfolded prions can cause various brain diseases, making healthcare difficult. Many benefits arise from dendrimers.<sup>68</sup> Dendrimers are highly branched nanoscale molecules with well-defined structures that are used for precise property control. This structural regulation allows the addition of phosphorus, which prevents prion infections.<sup>69</sup> Dendrimers may assist in the systemic administration of AD medicines. Recent research suggests that many factors limit the production of this product, notably its high production costs. Further research is required to understand the health effects of extended dendrimer exposure.<sup>70</sup>

## Micro/Nanoemulsions

Micro/nanoemulsions with 10–100 nm hydrophobic core-and-hydrophilic block copolymer shell structures can control anticancer drug release.<sup>71</sup> This unique shell design prolongs drug circulation and prevents drug-conjugated core-phagocytosis-complement cascade interactions.<sup>72</sup> Shells are ideal for PEG because they do not interact with serum proteins.<sup>73</sup> The lack of targeting moieties hinders polymeric micelle-based GBM treatment, which may enhance tumor formation.<sup>67</sup> Drinking water containing micelle-water-soluble coenzyme Q10 (Ubisol-Q10) in double transgenic AD mice. It improves long-term memory and lowers A plaques. Micro/nanoformulation helps target cells break down tau protein and activate autophagy.<sup>22</sup> Curcumin-loaded polymeric nanoformulations and bovine serum albumin glycation in phosphate-buffered saline reduce AD-mice amyloidogenesis.<sup>74</sup>

## Gold and Silica Nanoparticles

Nanomedicine has focused on Au NPs containing gold cores because of their advantages. These characteristics, including a high surface-to-volume ratio, blood-brain barrier penetration, and adjustable size, enable simple customization. AuNPs are among the most effective inorganic metal NCs for treating high-grade gliomas (HGG). The potential for treating HGG using AuNPs is limited because of their inability to target tumors.<sup>75</sup> Through the recent trapping of Au NPs via gold-sulfur interactions, the ability of a DNA aptamer to target the expression of EGFRvIII in GBMs has been enhanced, and this new complex has been demonstrated as a unique possibility for GBM therapy in vivo and in vitro.<sup>76</sup> AuNPs facilitate the delivery of targeted therapeutic genes.<sup>77</sup> For instance, it showed better sensitization of GMB cells in mice using a new Au-iron oxide NP to deliver therapeutic miR-100 when administered with systemic TMZ.<sup>57</sup> Clinical trials have been conducted for the treatment of HGG using a variety of AuNPs and chemotherapeutic drugs have been conducted.<sup>77</sup>

## Drug-Loaded Nanoemulsion

Recently, there has been a significant surge in interest in the chemical and biological properties of inorganic NPs falling within the size range of 10–1000 nm.<sup>78</sup> Drug delivery is promising because of the unique properties of NPs. These include their remarkable drug-carrying capacity, stability, controlled drug release, high selectivity in targeting cells or tissues, and the ability to transport hydrophilic and hydrophobic compounds. These advantages solve various problems associated with conventional drug delivery.<sup>79</sup> The release of drug-loaded NPs into the target region may occur through diffusion, degradation, erosion, or external energy input.<sup>80</sup> Targeted medication delivery frequently involves the use of ceramic NPs and proteins.<sup>38</sup> The two most important criteria to consider when choosing an efficient method to create varied-sized NPs are the easy-to-functionalize property and strong biocompatibility of the changed molecule.<sup>81</sup> The use of AuNPs provides a flexible platform for efficient drug delivery. By overcoming multidrug resistance (MDR), doxorubicin-coated AuNPs have shown improved drug accumulation in cancer treatment.<sup>82</sup>

## Carbon Nanotube (CNT)

At a nanoscale size of less than 100 nm, CNT exhibits advanced physical, mechanical, and high-aspect-ratio characteristics.<sup>83</sup> These factors significantly affect the cellular internalization of therapeutic compounds. Strategies for CNT functionalization include linking the carboxyl group after oxidation and adding an organic group to the sidewall or tip of the CNT.<sup>84</sup> Additionally, CNTs linked to polymers and dendrimers exhibit improved biocompatibility, increased solubility, and decreased aggregation.<sup>85</sup> Although acetylcholine-loaded SWCNT (single wall carbon nanotubes (SWCNTs)) have been investigated for AD treatment, and CNT with stem cell therapy have been employed in treating stroke, only a few investigations of CNT in CNS treatment have been documented.<sup>86</sup> The application of nanotechnology in biosciences and pharmaceutical businesses has been enhanced by modifying carbon nanohorns and nanodiamonds (CNT).<sup>87</sup>

## How Do Recently Developed Methods Target Brain Disorders?

### Scaffolds

Scaffolds of self-assembled peptide nanofibers have been investigated to enhance optic nerve regeneration.<sup>82</sup> Nanofiber scaffolds were naturally produced by the peptides at salinity concentrations.<sup>83</sup> Simple L-amino acids confer biocompatibility to these scaffolds.<sup>84</sup> To evaluate its applicability, in vitro brain neuron synapse formation and PC12 cell neurite outgrowth were supported by a nanofiber scaffold composed of Arg–Ala–Asp–Ala (RADA) peptides.<sup>85,86</sup> The quantity A scaffold, based on RADA (arginine-alanine-aspartic acid-alanine) enhanced axon regeneration across the lesion site in a hamster model of optic tract transection.<sup>65,87</sup> This demonstrated that the capacity of the optic nerve to regenerate persists even after damage. Notably, this function was not enhanced by nanoscaffold therapy. The absence of intact ganglion cell axons in the transaction scenario or neuronal injury from the Mn<sup>2+</sup> contrast agent are the two potential explanations proposed by the authors for the observed result.<sup>88</sup> However, optimizing nanofiber technology may help the CNS heal after injury, possibly in combination with other techniques that provide biological signals to regenerated axons.<sup>89</sup> The potential of the longitudinally structured nanoscaffolds for axonal regeneration was investigated. In one study, a nanofiber scaffold composed of gelatin and crosslinked dextran sulfate was employed.<sup>85</sup> This scaffold was



infused with human embryonic spinal cord cells, which enhanced the functional recovery in a rat spinal cord injury (SCI) model, including transection.<sup>90</sup> The reinforcement of the scaffold was also observed. Self-assembling nanofiber scaffolds are another topic of study in SCI.<sup>91</sup> Neural stem cell (NSC)-seeded scaffolds exhibit greater axonal innervation than nonseeded scaffolds. Animal implants using Schwann cell-seeded scaffolds showed significantly improved innervation compared with NSC scaffolds.<sup>92</sup>

### 3D Printing

Improvements in 3D printing technology and the creation of custom biomaterials have enabled the precise fabrication of biological components and intricate 3D geometries precisely.<sup>88</sup> CNS is vulnerable to several types of harm, including neurodegenerative disorders such as AD, PD, stroke, accident-related injuries, and brain cancer.<sup>89</sup> With 3D printing, the peripheral nervous system (PNS) and nerve guidance conduits (NGCs) may be efficiently repaired, minimizing scarring and nerve compression, while serving as a bridge to replace larger gaps.<sup>90</sup> A Fickian diffusion process causes the release of levodopa from the 3D-printed scaffolds over 14 days through MTT analysis, fluorescence microscopy, and SEM tests; mesenchymal stem cells (hAD-MSCs) generated from human adipose tissue were employed, and these techniques successfully verified appropriate biocompatibility. Overall, the results demonstrate that neural tissue engineering applications can employ PLA/CS 3D-printed scaffolds as a substitute for the levodopa delivery method for PD.<sup>91</sup>

### 4D Printing

Current printing technologies struggle to achieve nanoscale 3D printing. Nanocomposites, host material matrices with NPs, are the focus of 3D printing nanomedicine research. 3D printing has evolved owing to rapid advances in material science and additive manufacturing. Therefore, 4D printing has improved significantly. Time, which is the fourth dimension, allows 3D-printed objects to be distorted after printing. This fast-growing technology has produced dynamic and adaptable products that respond to external inputs. The applications and effects of AM are being studied.<sup>92</sup> 4D printing can be performed in two ways. One possibility is to include the transformation of information into the structural design. Using this technique, heterogeneous ink components are precisely positioned within multiple layers, enabling printed objects to self-morph.<sup>93</sup> Alginate hydrogels allow for the effective bioprinting of Schwann cells, which express neurotrophic factors and help with peripheral nerve regeneration.<sup>94</sup> Nanomaterials' unique physical and chemical properties of nanomaterials have drawn attention to their potential to advance 4D printing.<sup>95</sup> Nanomaterials can change the shear thinning of bioinks, thereby enabling 4D printing. The medical applications of 4D printing, particularly in tissue regeneration, are noteworthy. Scaffold manufacturing for this purpose must be explored further. Tissue regeneration involves spontaneous changes that can affect functional recovery.<sup>95</sup> 3D printing can create tissue scaffolds with complex geometries and microarchitectures; however, natural tissue regeneration mechanisms cannot be replicated. Stimuli-responsive 3D tissue constructs were produced using 4D printing. This discovery potentially replicates the tissue regeneration dynamics. Owing to cell traction stress, 4D metamorphosis may affect cell shape, orientation, density, and cell-to-cell communication. Therefore, tissue regeneration may benefit from these actions.<sup>96</sup>

### 5D and 6D Printing

The terms "5D" and "6D" printing refer to theoretical expansions of 3D printing that include the addition of dimensions to the printing process beyond the standard three spatial dimensions (x, y, and z). These technologies have the potential to markedly change the design and creation of complex structures, including biological tissues; however, they are still in the research stage and have not yet been extensively implemented. Precisely controlling printing parameters such as temperature, pressure, and speed is crucial to ensure optimal cell viability and functionality in 5D printing.<sup>97</sup> Time and material properties are additional dimensions in 5D printing, meaning that the printed object can change over time or in response to different stimuli such as temperature, humidity, or light.<sup>98</sup> The focus is on leveraging the more proven 4D and 5D printing processes to make biomaterials, although the idea of 6D printing is relatively new. Theoretically, combining 4D and 5D techniques in a coordinated manner can result in 6D printing. However, practical implementation is currently not feasible owing to insufficient knowledge and production capacity. Finding or creating the best material

that is both stiff and responsive to one or more stimuli is the biggest challenge. The creation of structures with extra dimensions, such as topology and texture, is made possible by 6D printing, which can improve the mechanical, biological, and physical qualities of printed tissues.<sup>99</sup>

## How Do Nanotechnology-Based Therapeutic Approaches Target Brain Disorders?

### Nano-Immunotherapy

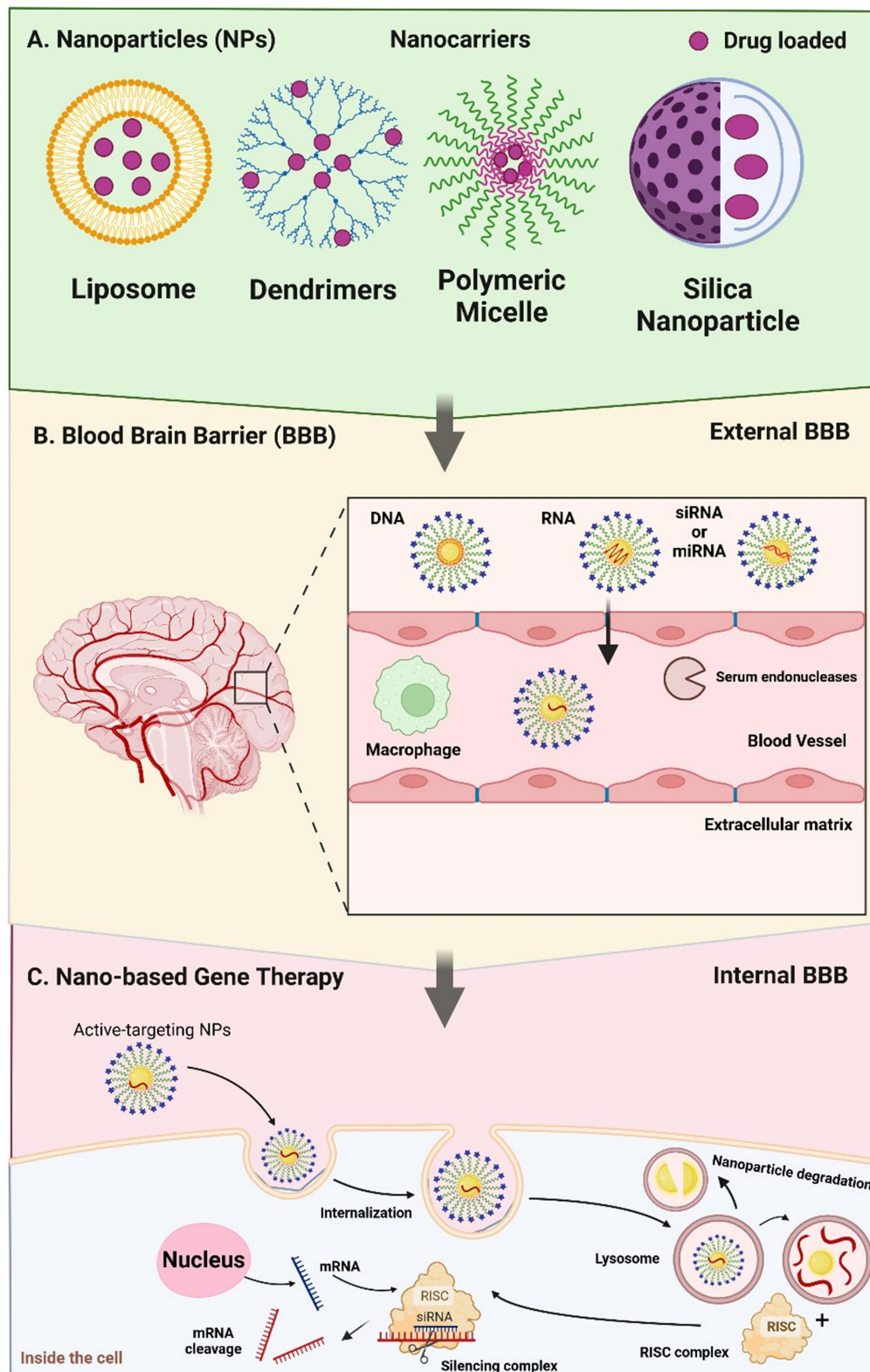
Therapeutic approaches targeting the immune system have achieved significant clinical success. Through the active detection and eradication of malignant cells, the immune system can inhibit.<sup>100</sup> Nano-immunotherapy has become a viable approach to maximize the uptake of therapeutic drugs in brain disorders and decrease off-target damage, nano-immunotherapy has become a viable approach.<sup>101</sup> Nanomaterials can assist in changing how biologics interact with target immune cells, resulting in the accumulation of these immunomodulators in brain disorders and the surrounding microenvironment.<sup>12</sup> Nanomaterials can also target immunomodulators in brain disorders.

### Nano Gene Therapy

Gene therapy has recently gained attention as a potential treatment for brain disorders caused by genetic mutations (Figure 3).<sup>12,102</sup> Small interfering ribonucleic acids (siRNAs) and micro-ribonucleic acids (mRNA) can be used as therapeutic agents to modify gene expression with high specificity. For example, siRNAs can increase the susceptibility of cells to low molecular weights.<sup>103</sup> A standard intracerebral injection may result in neurological injury and inadequate transgene expression due to the BBB.<sup>104</sup> Several delivery methods have been reported for glioblastoma multi-forme gene therapy (Figure 3).<sup>105</sup> A non-viral gene delivery strategy targeting angiogenesis has been established for effective gene therapy without harming healthy brain regions.<sup>106</sup> Temporary gene transfer was accomplished using cationic microbubbles that were VEGFR2-targeted and exposed to focused transcranial ultrasound. Cationic microbubbles have been advertised for their high affinity and efficiency in loading DNA into cells of brain disorders in vitro.<sup>104</sup> Recent advances in nano carrier-based gene therapy have enabled scientific organizations the capability and motivation to assess a wide range of prospective therapeutic options (Figure 3).<sup>107</sup> In this context, nanomaterials as gene carriers have significantly increased the efficacy of gene therapy and minimized the enzymatic degradation of genetic components.<sup>108</sup> They initially researched in vivo gene delivery to brain disorders using organically modified silica NPs (ORMOSIL) (Table 2).<sup>109</sup> Numerous studies are being conducted to develop gene therapy approaches for treating neurological illnesses. Figure 3 shows that gene therapies have to cross the BBB to be effective. The endothelial membrane forms a biological barrier in the brain vasculature. To prevent the passage of chemical substances, such as toxins and harmful microbes, endothelial cells are joined together by tight junctions.<sup>110,111</sup>

Interdisciplinary integration of efforts to build nanotechnology will help elucidate the function of neural circuits and devise methods for diagnosing and treating brain illnesses.<sup>119</sup> In AD, encapsulated synthetic NPs of poly(lactide-co-glycolic acid) is used as an effective agent. Similarly, in vitro studies have shown that polymeric NPs increase drug delivery to the brain and reduce oxidative stress, inflammation, and plaque burden.<sup>120</sup> Poly(ethylene imine)-based NPs are used for delivering genes for gene therapy in brain cancer, including poly(ethylene imine)-poly(L-lysine) as a copolymer reported as a gene delivery systems, and in vitro studies have shown that the incorporation of L-glutathione acts as a backbone for poly(ethylene imine), which increases cytocompatibility and improves the ability of the polymer to cross the BBB.<sup>121,122</sup> Additionally, liposomes are considered carriers for gene therapy. Liposomes and mannitol act as delivery systems to transfer oligonucleotides for treatments that would cross the BBB in brain cancer.

Similarly, a PEGylated dendrigraft poly-L-lysine was used to develop a multifunctional NC that could carry desired peptides and genes to the brain via systemic injection (Table 2).<sup>123</sup> Solid lipid NPs and coated and non-coated chitosan were used to transfer siRNA from the nose to the brain via the trigeminal and olfactory nerve routes. A Caco-2 epithelial cell model was used to release siRNA, which successfully entered the monolayer to target BACE1.<sup>124</sup> In another study, PEGylated magnetic NPs were utilized to deliver the siRNA to nerve cells by endocytosis to suppress the BACE1 gene



**Figure 3** Nanotechnology in gene therapy and blood–brain barrier penetration for brain disorder: **(A)** Represents of nanoparticles, nanocarriers, and drug-loaded NPs, **(B)** Mechanisms of blood–brain barrier transfer: Several endogenous compounds use receptor and adsorption-mediated endocytosis and carrier-mediated pathways, which allow NPs carrying medicines to cross the blood–brain barrier and enter the brain and **(C)** Nano-based gene therapy in the internal blood–brain barrier.

**Table 2** Multiple Routes of Nano Pharmaceuticals in Treating Brain disorders

S.I No	Brain Disorder	Nanocarrier Loaded with Drug	Mode of Administration	Drug release Mechanisms	Findings	References
1	Alzheimer's Disease	Donepezil through Chitosan Nanofiber	Intramuscular	Receptor-mediated endocytosis	Donepezil is promptly released	[64]
		Rivastigmine through Polymeric NP			Enhanced rivastigmine administration for treatment and prevention	
		Galantamine hydrobromide through solid lipid nanoparticle	Oral Intravenous	Transcytosis	The effectiveness and safety of nasal CX-NP2 intracellularly in brain neurons in vivo	
		Estradiol with PLGA NP			It prevented the hippocampal area of the brain from expressing A $\beta$ 42 immunoreactivity	
2	Parkinson's Disease	Levodopa-loaded polyacid nanoparticle	Intragastric	Absorption	It improved therapeutic efficacy and bioavailability	[112]
		Rotigotine loaded Chitosan NP	Intranasal			
		Ropiniroleloaded PLGA microspheres	Intranasal			
3.	Stroke	Tissue Plasminogen	Intra Arterial Sheath	Absorption	It improved neurological and functional recovery after Stroke and reperfusion.	[113]
4.	Brain Cancer	Doxorubicin-loaded poly copolymer	Pulmonary Delivery	Transport, absorption, and endocytosis via receptors	Possible economically viable and effective treatment	[114]
5.	Epilepsy stroke	LDL -Cholesterol Conjugates	Nasal, Oral Parenteral, rectal, and respiratory	Absorption	Site-specific administration improves thrombolysis	[115]
6.	Psychotic c disorder	Anxiolytic and antipsychotic agents	Oral, transdermal, topical, I V	Degradation and environmental stimuli	Possibly transport drugs from nose to brain	[116]
7.	Multiple Sclerosis	Tempamine loaded LiposomeLiposome	Pulmonary Delivery, intravenous	Adsorption, fusion, and diffusion	Cerebral uptake increases	[117]
8.	Glioblastoma	Temozolomide	Intravenous	Adsorption, fusion, and diffusion	Potentially transport drugs from nose to brain	[118]

and reduce A $\beta$  production.<sup>54</sup> They examined the viability of using cutting-edge technology to compress DNA plasmids into NPs and send them to the brain to slow or stop neurodegeneration in an in vivo model of PD.<sup>125</sup>

Similarly,  $\alpha$ -synuclein is embedded in multifunctional magnetic NPs containing a small hairpin RNA, and it efficiently repairs PD.<sup>126</sup> Gene therapy is beneficial owing to its ability to deliver gene therapy medications to target brain areas that can alter functions and cure PD without causing side effects.<sup>127</sup> CRISPR-Cas9 was used to knock out Vps35 in exon 15 of the mouse *PARK17*. This has a direct impact on easing PD symptoms by considerably reducing the

release of dopamine from the substantia nigra in the middle of the brain.<sup>128</sup> Superparamagnetic iron oxide NPs (SPIONs) are used as nanovehicles for cell tracing and gene therapy in stroke.

## How Do BBB Crossing Strategies Use Nanomaterials?

NPs are advantageous in medical delivery owing to their numerous advantages, including extended bloodstream circulation, regulated medication release, enhanced stability, high drug-loading capacity, and targeted delivery (Figure 3). Consequently, the potential of nanomaterials for transferring therapeutic medications across the BBB has been thoroughly investigated.<sup>129</sup> The size, zeta potential, and hydrophilicity of nanomaterials have a major impact on their in vivo.<sup>130,131</sup> Nanomaterial-based BBB crossing mechanisms and strategies, BBB transportability study techniques, and treatment for NDs, such as AD and PD, frequently fail because chemicals have trouble entering the brain due to the BBB.<sup>132</sup> Numerous drug delivery techniques demonstrate the successful transportation of diverse pharmaceutical agents across the BBB using nanomaterials.<sup>133</sup> This study used nanomaterials to demonstrate and analyze ways to bridge the BBB.

## Intranasal Delivery

The intranasal route of drug delivery is a productive and non-invasive method for delivering medications to the brain, circumventing the challenges associated with parenteral administration.<sup>134</sup> By employing an intranasal administration method, drugs can be efficiently transferred to the brain through the olfactory mucosa.<sup>135</sup> This can occur by traversing the connective tissue surrounding the olfactory nerve bundle or the axons of olfactory neurons, thereby circumventing the BBB.<sup>136</sup> Intranasal administration has successfully circumvented hepatic first-pass metabolism, reduced drug accumulation in non-target tissues, and mitigated systemic side effects.<sup>137</sup> Furthermore, intranasal administration has emerged as a widely utilized approach in pharmaceutical delivery owing to several benefits, including prompt absorption, rapid initiation of action, noninvasive nature, minimal tissue damage, and straightforward application.<sup>138</sup> This study revealed significant variations in the effectiveness of drug delivery among different intranasal delivery nanomaterials. These variations were mostly independent of the physicochemical features of the pharmaceuticals delivered.<sup>139</sup>

## Temporary Disruption of the BBB

Temporary rupture of the BBB has been extensively investigated as a prominent strategy for facilitating the delivery of medications from the circulatory system into brain disorder.<sup>140</sup> The methods used to disrupt the BBB mostly involve osmotic, ultrasonic, and magnetic disruption.<sup>132</sup>

## Local Delivery

Numerous studies have been conducted on the direct administration of medications for local brain disorders. Numerous procedures involving localized delivery of various therapeutic drugs have been established. Early research on local non-drug delivery into the CNS mostly used the implantation of biodegradable polymer wafers with a pharmacological payload.<sup>141</sup> These wafers are designed to release drugs in a controlled manner over an extended period, leading to enhanced therapeutic outcomes.

## Cell-Penetrating Peptide-Mediated Blood-Brain Barrier Crossing

Cationic cell-penetrating peptides (CPPs) are short and amphipathic and have cationic properties.<sup>142</sup> Several peptides have been shown to increase the translocation of conjugated drugs or biomaterials through cell membranes.<sup>143</sup> There are two primary categories of cationic CPPs: Antimicrobial sequences and chimeric peptides.<sup>144</sup> Although the precise mechanism by which CPPs facilitate cell membrane transportation remains unclear, it is believed that electrostatic interactions between the cationic charges present on CPPs and the surfaces of brain endothelial cell membranes play a crucial role in enabling the transport of CPP-modified nanomaterials across the BBB.<sup>145</sup>

## Receptor-Mediated BBB Crossing

The receptor-mediated transcytosis pathway transports numerous endogenous macromolecules into the brain.<sup>146</sup> The interactions between ligands and their corresponding receptors on the surface of brain endothelial cells (BECs) facilitate



vesicle formation through endocytosis pathway.<sup>147</sup> Subsequently, the vesicles release ligands, allowing them to cross the BBB and enter the CNS via exocytosis. This allows the ligands to perform their biological roles in the CNS.<sup>103</sup>

## Shuttle Peptide-Mediated BBB Crossing

There is accumulating interest in shuttle peptides owing to their cost-effectiveness, abundant availability, diminished immunogenicity, and notable chemical adaptability, such as their compatibility with chemical alterations.<sup>10</sup> Shuttle peptides facilitate the translocation of diverse payloads across the BBB, encompassing tiny molecules, genetic material, proteins, and NPs.<sup>148</sup> Numerous BBB shuttle peptides have been devised to facilitate the transport of NPs, thereby enhancing their dispersion within the CNS.

## BBB Crossing Mechanism

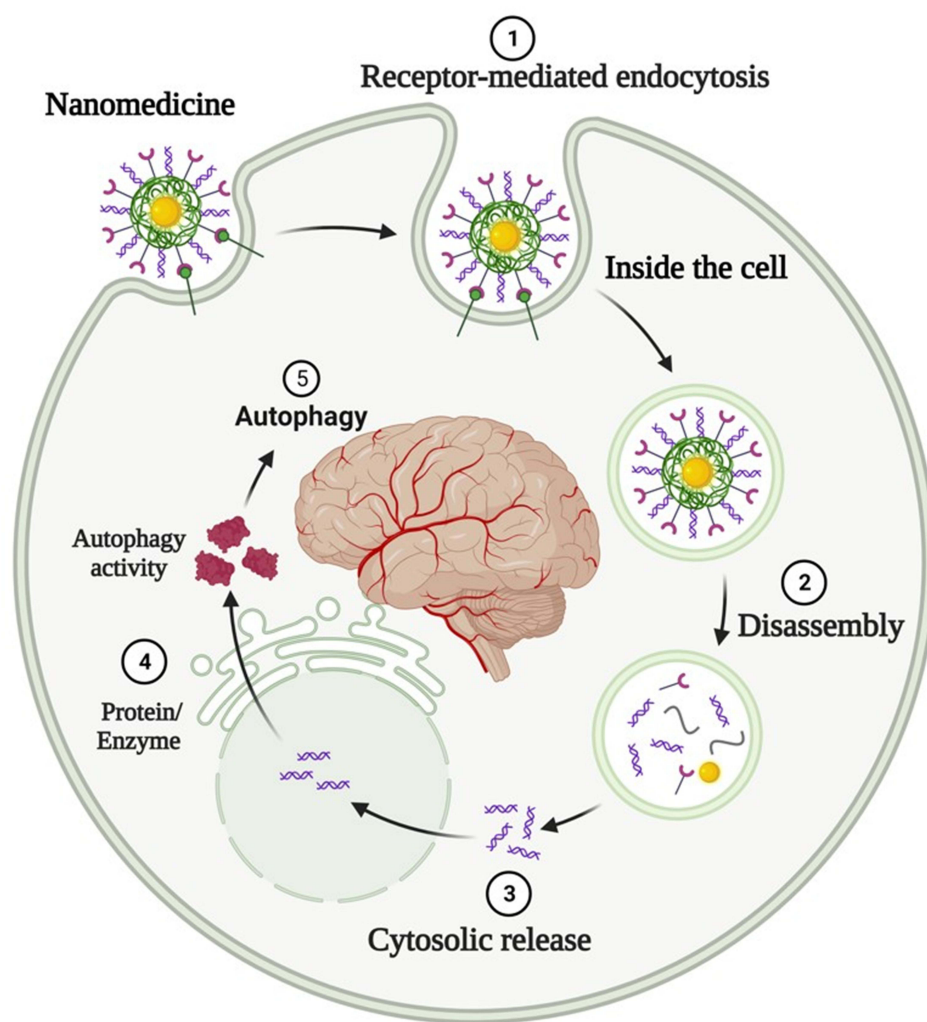
The BBB, blood–CSF barrier (BCB), and arachnoid barrier are the three major interfaces formed by distinct cells. Microvascular endothelial cells that line the cerebral capillaries and enter most mammalian brains, spinal cords, and other organisms with a fully developed CNS constitute the BBB. Given that the average adult total surface area falls between 12 and 18 m<sup>2</sup> and the average microvessel surface area per gram of tissue is between 150 and 200 cm, it is regarded as the largest interface for blood–brain exchange. BBB is essential for shielding the brain parenchyma from blood-borne pathogens and acts as a formidable barrier against the entry of medications and other exogenous substances into the CNS.<sup>149</sup>

Three methods—non-invasive, invasive, and identifying alternate drug delivery pathways—can transport a nanomaterial-based BBB throughout the brain.<sup>150</sup> Noninvasive methods widely used in research depend on biological processes to help drugs pass through transcellular channels and the blood-brain barrier (Figure 3).<sup>151</sup> The intranasal delivery method effectively crosses the BBB by delivering NPs through the olfactory epithelium or trigeminal nerves directly into the BBB.<sup>152</sup> However, this is challenging for large proteins to do so. With low cellular toxicity and high effectiveness, cell-penetrating peptide (CPP)-based delivery methods can successfully transport macromolecules across cellular membranes.<sup>138</sup> The BBB must be physically broken apart for the invasive mechanism to function, and nanomaterials must be transferred along paracellular channels to cross the BBB (Figure 3).<sup>153</sup> The transient BBB disruption technique described above and local delivery strategy are part of the invasive mechanism, also known as the paracellular mechanism.<sup>154</sup> In the non-invasive approach, the BBB is unaltered during the drug delivery process, and NPs are delivered across the BBB via transcellular channel.<sup>155</sup> Noninvasive or transcellular intranasal delivery strategies include four BBB crossing methods: CPP-mediated, receptor-mediated, shuttle peptide-mediated, and cell-mediated.

In contrast, invasive procedures manipulate the BBB or directly administer medications to the brain tissue.<sup>156</sup> Various methods have been used in invasive research, including intracerebral implants and intraventricular, intrathecal, and interstitial deliveries. Researchers have targeted medications for convection-enhanced delivery. The use of osmotic methods to cross the BBB is invasive. Pharmacological and ultrasound-mediated BBBD have also been used in invasive research.<sup>1</sup> S-mediated BBBD uses hyperosmotic solutions, concentrated ultrasound, and magnetic fields to shrink endothelial cells and destroy tight junctions, allowing molecules to cross the BBB.<sup>157</sup>

## Nano Protein/Enzyme Replacement Therapy

NPs can incorporate moieties into a single therapeutic molecule, making them potential treatments for brain diseases. This method delivers multiple medicinal molecules simultaneously, improving the treatment efficacy.<sup>158</sup> The chemical and biological features of NPs make them the most versatile delivery options. NPs comprise lipids, polymers, dendrimers, and inorganic compounds. The core material used to finely regulate the NP size, shape, charge, binding capacity, and hydrophobicity/hydrophilicity (internally and externally) is crucial.<sup>125</sup> The relationship between these parameters and the pharmacokinetic half-life, biodistribution, stability, and binding capability of therapeutic proteins or enzymes has been thoroughly examined (Figure 4).<sup>14,159</sup> When coupled with seq-containing proteins, the cationic tail promoted NP production.<sup>8</sup> The potential use of these particles with many therapeutic proteins is crucial for their study and development. However, healthy mouse models have shown that targeted NPs accumulate in the brain, similar to non-targeted NPs.<sup>160</sup> The study reported uptake into proinflammatory Th17 cells with no harmful effects at all doses. Compared to nanospheres alone, nanospheres reduced interleukins and improved clinical scores (Table 3).<sup>161</sup> However, these studies



**Figure 4** Nanotechnology-Enhanced protein/enzyme therapy mechanisms in Brain Disorders. Depending on the physicochemical characteristics of the drugs, drug nanocarriers are successively delivered to the endosomes after internalization, recycling endosomes, acidic lysosomes, mitochondria, or the nucleus.

did not include long-term observations. Nevertheless, nanospheres affect different body regions, triggering a brain reaction to autoimmune disorders.<sup>162</sup>

Nasal medication delivery has been proposed to improve the delivery of protein-loaded NP brain delivery. This procedure is less intrusive than a direct injection.<sup>168,169</sup> This approach must meet certain criteria to be deemed viable. Nasal administration, such as direct injection, bypasses first-pass clearance and allows therapeutic drug distribution to the CNS via the olfactory bulb and brainstem.<sup>170</sup> The co-administration of matrix metalloproteinase-9 (MMP-9), a chemical that increases nasal epithelial permeability, increases the efficiency of brain medication delivery. The therapeutic chemical was delivered twice to the midbrain and cortex, and three times to the brainstem. However, nasal delivery systems have several disadvantages. Previous studies have found that the administration of nasal medication is hindered by nasal epithelial absorption and brain tissue transfer (Figure 4). The improved delivery strategy reduced stroke infarct size by 50% and increased life expectancy by 21 days compared to intravenous and intranasal exosome administration (Table 3).<sup>171</sup> Fluorescence imaging showed that intranasal administration resulted in a much higher absorption rate than intravenous administration. Active microglial cells were reduced to levels comparable to control animals.<sup>172</sup> However, therapeutic applications of these improvements are limited. Thus, the treatment of brain disease must be improved.<sup>173</sup>

**Table 3** Some Brain Disorder Drug Delivery Features of Nanoparticles with Patents

S. No	Patent Number	Patent Title	NPs	Size	Drug	Mode of Administration	Applications	Drug delivery mechanism	Drug Release Mechanism	Disease	Summary of the Inventions	References
1	US20100173004	Preventive and therapeutic vaccine for Alzheimer's Disease	Polymeric nanoparticle (PNP)	10–1000	PLGA encapsulated NMDA-NR1 vaccine	Subcutaneous, intravenous, and oral	The PLGA particle is a possible treatment for neurodegenerative Disease	Transcytosis	Degradation of polymer through enzymatic reaction	Alzheimer's disease	The NMDA-NR1 protein DNA containing PLGA particle for oral vaccination to produce steady antigen-specific serum antibody responses with possible therapeutic applications in neurodegenerative diseases	[163]
2	US20110027351	pH-sensitive polymeric micelles for drug delivery	Liposome	< 100	Folate	Pulmonary Delivery, Intravenous	pH-sensitive mixed micelles for targeting drug delivery	Endocytosis	Endocytosis and adsorption to cell surface bursting due to environmental stimuli	Parkinson's disease	The mixed micelles are pH-sensitive and release drugs when they are in an acidic tumor microenvironment. These micelles combined with target moieties like folate for a precise drug delivery system.	[164]
3	US20060222716	Colloidal solid lipid vehicle for pharmaceutical use	Solid Lipid nanoparticle (SLNs)	50–1000	Low-density Lipoprotein (LDL) NPs	Nasal, oral, parenteral, rectal and respiratory	It establishes a drug delivery system that permits the regulated release of biologically active compounds across several administration pathways.	Absorption	Supersaturation of SLN drug conjugates at high-cooling	Epilepsy, Stroke, Trauma, and Alzheimer's disease	The SLNS includes a colloidal drug delivery mechanism and tocopherol or its derivatives for drug administration. It tries to load biologically active substances, particularly antibiotics that are water soluble and provides regulated drug delivery through a variety of administration modalities.	[165]

4	US20070237827	Nanoparticles for drug delivery	Polymeric nanoparticle (PNP)	10–1000	Chitosan-coated erythropoietin in (HMG-Co-A reductase inhibitors)	Subcutaneous, intravenous, and oral	The PNP provides an opportunity to enhance medication absorption through intestinal and blood-brain barriers.	Receptor-mediated endocytosis	Swelling of PNP via diffusion	Brain targeting	Chitosan, poly-glutamic acid ( $\gamma$ -PGA), and bioactive substances improve the paracellular drug delivery process, particularly when given orally and for the regulated Disease of different bioactive substances against Alzheimer's.	[166]
5	US20090148417A1	Carbon nanotubes serve as stem cell scaffolds	Carbon nanotubes	3.5–70	Stem cell loaded CNT	Intraperitoneal and intravenous	Using non-toxic carbon nanotubes enhanced the stem cell treatment scaffold and increased the contact between differentiated stem cells and the target tissues, improving the effectiveness of the therapy.	Endocytosis and diffusion	Electrically or chemically controlled	Parkinson's disease	A non-toxic carbon nanotube scaffold that dramatically boosts the ability of stem cell treatment to encourage tissue regeneration	[161]
6	US7682627	Artificial low-density lipoprotein carriers for transport of substances across the blood-brain barrier	Solid Lipid nanoparticle (SLNs)	50–1000	LDL-cholesterol conjugates	Nasal, oral, parenteral, rectal and respiratory	It is an efficient way to transport drugs across the blood-brain barrier, improving drug stability and accuracy and boosting the treatment of many brain illnesses and disorders.	Absorption	High-pressure homogenization causes dispersed molecular drugs in a solid solution.	Alzheimer's disease and Parkinson's disease	Drug integrity is maintained while transported across the BBB because of the structural stability of LBL particles, which guards against endogenous esterases from degrading therapeutic compounds conjugated with cholesterol.	[167]

The physical properties of NPs make them suitable for encapsulating enzymes. The stability, cellular uptake, and activity of enzyme-loaded NPs have been extensively explored.<sup>174,175</sup>

However, the development of enzyme-loaded NPs for brain administration has been limited compared liposomes, PBCA, and PLGA NPs.<sup>168</sup> anti-NR1-SODPBCA NPs were targeted using an antiNMDA receptor 1 antibody. In this study, the antibody levels varied significantly between the vehicle types. Notably, all particles accumulated in the brain. This caused a 50% reduction in infarct size in the mouse ischemia model. GNeo-NHS-modified 1,2-dioleoyl-snglycero-3-phosphoethanolamine (DOPE)<sup>176</sup> was encapsulated with positive and negative charges in another liposome. Fibroblasts were treated with L-iduronidase to examine the effects of glycosaminoglycan. Effective targeted strategies to help these NPs breach the BBB are needed to advance in vivo investigations.<sup>177,178</sup>

## How is One Possible Therapeutic Approach Individualized Through Nanomedicine?

Tailored nanomedicines have gained considerable scientific interest in recent years owing to their considerable potential for safe, precise, and regulated drug administration across the BBB, tailored nanomedicines have gained much scientific interest in recent years.<sup>85</sup> Tailored nanomedicines may offer many advantages in treating brain disorders and neuro-AIDS problems.<sup>179</sup> In addition to on-demand drug release, personalized medicine is appealing because it allows precise adjustment of the therapeutic dose for each patient.<sup>180</sup> Additionally, the incorporation of longitudinal monitoring techniques can support the tracking of patient responses to therapeutic interventions, drug doses, and treatment protocols, enabling doctors to customize their treatment plans.<sup>181</sup> Personalized nanomedicines offer significant potential to achieve maximal efficacy with the least side effects, regardless of whether they are used to treat brain disorders.<sup>182</sup> The development of stimuli-responsive nanomedicines, which include biological, chemical, physical, dual, and multi-responsive forms, has enabled site-specific accumulation and triggered drug release.<sup>183</sup>

Furthermore, studies on the application of prodrug-based nanomedicines have provided several benefits, including better drug loading efficiency, increased targeting capacity, real-time control, and reduced risk of side effects.<sup>132</sup> Several events can activate nanomedicines. Nanomedicine steric shields built of stimuli-responsive cleavable polymers can prolong tumor circulation and effectively administer medication to target cells. Table 3 shows that patents approved by the FDA and NIH have created a customized medicine roadmap to transform healthcare. Personalizing patient treatments and interventions is the goal of this research to change healthcare. These companies use genomes, technology, and data analyses to improve healthcare accuracy, targeting, and patient centricity. These esteemed university partnerships show that personalized medicine is a promising way to satisfy healthcare needs and improve health outcomes.<sup>184</sup>

## Aspects of Nanomaterials and Nano Therapies' Biosafety

The unique physicochemical features of nanomaterials can improve brain cancer treatment.<sup>12</sup> Nano-pollution results show that NPs are easily absorbed by cells owing to their small size. Soft NPs made of polymers and liposomes have gained regulatory permission for clinical use and have demonstrated promise in nanomedicine.<sup>185</sup> In contrast to their use as therapeutic agents, NPs are mostly studied as delivery agents, and the effects of NPs on biological systems after administration and their removal still need to be thoroughly studied.<sup>186</sup> Before NPs are used in clinical settings, it is important to study several preclinical and clinical trial design problems such as immediate and long-term stability, tolerability, biodistribution, and elimination of NPs.<sup>187</sup> Publications on clinical trials of nanomedicine that are currently available generally concentrate on the therapeutic effectiveness of pharmaceuticals, ignoring the potential negative consequences of NPs on human health.<sup>188</sup> The NanoTherm<sup>®</sup> therapy was developed by a German company named MagForce. It employs magnetic hyperthermia and radiation to destroy cancer cells using a ferrofluid consisting of superparamagnetic iron oxide NPs.<sup>72</sup> Nanotherms provided an average survival of 13.2 months in a clinical trial involving 60 patients, compared to 6 months with standard care.<sup>189</sup> As the FDA has not provided any guidelines for particular nano-based products, regulatory authorization of nano-therapeutics presents additional, significant obstacles.<sup>190</sup> Currently, the conditions used have been steadily established under regulations on bulk commodities. The monitoring



results for nanoformulated medications are based on a discrete assessment of benefits and risks, which creates a difficult position and delays commercialization.<sup>12</sup>

However, the lack of regulatory rules and standards for engineered nanomaterials is a crucial issue that must be addressed.<sup>191</sup> National/international agencies must make thoughtful decisions and forward them to create recommendations that can help researchers investigate potential medicinal applications. Additionally, it is crucial to create interdisciplinary partnerships based on public and private experts to advance the translational elements of nanomedicines while considering the clinical environment.<sup>192</sup> Notably, as already mentioned, strong partnerships and the standardization of nanomedicine as a form of treatment entail investigating the physiological aspects of drug NCs, the effects of differential stimulation of biological functions, increased efficacy, absence of adverse effects, and knowledge of the benefits of nanomedicine.<sup>193</sup> These factors will be crucial in bridging research gaps and facilitating successful translation from laboratory to clinical settings.

## Challenges and Alternative Approaches

The development of multifunctional nanomaterials with specific and tunable features for nanotherapeutics has created substantial obstacles that require immediate attention.<sup>12</sup> Building on decades of progress, nanotherapies for brain disorders are predicted to alter healthcare systems. The methodologies and achievements of nominal cancer nanotherapeutics have limitations and problems.<sup>194</sup> Several nanoformulations have been used in clinical studies. Their efficiency, biocompatibility, minimal side effects, and low toxicity distinguish these formulations.<sup>195</sup> Biochemical classification includes organic and inorganic NCs is currently being tested in preclinical trials to improve survival and decrease tumor growth.<sup>196</sup> NanoTherm<sup>®</sup>, developed by German business Magforce, has advanced cancer treatment. This novel treatment uses magnetic hyperthermia and radiotherapy to target and kill cancer cells using superparamagnetic iron oxide NPs, specifically ferrofluid.<sup>197</sup> In a clinical trial of 60 patients, nanotherms improved survival by 13.2 months compared with 6 months with conventional treatment.<sup>136</sup> The National Library of Medicine ClinicalTrials.gov database lists 2236 brain cancer. Two-hundred thirty-eight of these studies used nanotechnology in their study. A preliminary clinical trial of 10 individuals tested 89Zr-cRGDY ultrasmall silica particles. This study aimed to determine whether these particles could track brain disorder.<sup>198</sup> Nanomaterial fabrication and characterization must be carefully considered when building drug delivery systems<sup>199</sup> to reduce NC toxicity in healthy cells. This organized and defined process evaluates the advantages and disadvantages of these medications. Due to its intricacy, this evaluation can take time, delaying drug commercialization. The widespread use of multifunctional nanoplateforms is expected to exacerbate technological challenges.

## Future Prospectives

Drug-loaded NC spose many challenges to researchers and deregulatory organizations. Robust characterization techniques, including optimization of methodologies, safety regulations, and stability upkeep, are required to address these issues.<sup>200</sup> Recently, artificial intelligence (AI) has helped to improve NCs for neurological illnesses, which will help focus this issue known as “computational pharmaceuticals”, created due to the exponential rise in computer power and algorithms over the previous ten years. Recently, AI and multiscale modeling has been used, suggesting a potential shift to drug delivery systems. NCs are advantageous for directing medications to certain cells or tissues, preventing toxicity, and triggering healthy cells.<sup>201</sup> The size, shape, chemical composition, and surface characteristics of NCs play a role in how well they carry drugs. However, developing ideal nanocarriers for drug delivery is difficult.<sup>202</sup> AI-based computational methods can help optimize the drug loading, retention, and stability of NCs. The majority of the focus of molecular modeling studies for nanocarrier-based drug delivery systems has been (i) analyzing the development and structure of NCs, (ii) assessing the interactions and distribution of NCs, (iii) assessing the surface qualities of nanocarriers, and (iv) the adsorption of nanocarriers onto various surfaces.<sup>203</sup>

Furthermore, each NCs can be improved to exhibit the desired behavior. Thus, creating a repository that aids in identifying a suitable NCs scaffold and its functional groups for encapsulating and releasing a particular medication is a significant advancement. In the “Collaboratory for Structural Nanobiology”, efforts have been undertaken to establish a database repository of NCs, where scientists may access the 3D structures and physical and chemical characteristics of NCs.<sup>204</sup> NanoAmpere is a comprehensive database that details the security.<sup>205</sup> Although computational research and AI

will never replace laboratory experiments, they play a crucial role in speeding up and improving target and drug discovery processes, as well as inventing new, powerful computational tools for DDS simulation and NPs, which are constantly evolving. Unique regulations are required for the industry because of the potential implications for the global economy and the necessity to provide safety evaluations for nanomedicine therapy in neurological disorders.

In conclusion, there is a need for standardized norms and controls for NPs. To address this concern, national and international organizations must make informed decisions and establish comprehensive criteria for the use of nanomaterials in medicinal applications. Researchers in this field will significantly benefit from these guidelines. Interdisciplinary collaboration between the public and private sectors is also necessary to translate nanomedicine into clinical practice, particularly in healthcare. Major research fields include the ongoing pursuit of nanomedicine therapy standardization and robust cooperation. These studies examined the physiological effects and biological activities of drug NCs to enhance their biological efficacy and safety. Raising awareness about the benefits of nanomedicine is crucial for translating research findings into clinical practice. This comprehensive study summarizes the significance of nanotechnology in various therapeutic approaches including immunotherapy, stem cell therapy, gene therapy, and tailored nanomedicine for brain disorders. This review emphasizes that the unique physicochemical features of NPs can overcome obstacles in drug-free therapies, such as photodynamic treatment (PDT) and radiation, address challenges such as radio-resistant treatment, and reduce mortality risks. However, it is imperative to consider the biosafety of nano-assisted medicines prior to clinical translation. Assessing factors such as biodistribution, pharmacokinetics, and toxicity is crucial for the safe use of these medicines. In summary, interdisciplinary collaboration, awareness, and biosafety considerations key to advancing nanomedicine toward practical clinical applications.

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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.

## Disclosure

The authors declare no conflicts of interest in this work.

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