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REVIEW

Nanotechnology-Driven Drug-Delivery Systems: Mechanistic Insights for Pediatric Autism Treatment in 2026

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Abstract: Autism spectrum disorder (ASD) is a diverse neurodevelopmental disorder that commences in early childhood, characterized by enduring social-communication challenges, limited interests, and behavioral rigidity. The management of ASD continues to pose significant difficulties in pediatric practice. Converging evidence implicates abnormalities in synaptic scaffolding and transmission, excitation–inhibition imbalance, mTOR/PI3K–AKT signaling, neuroinflammation, gut–brain axis, and metabolic disturbances, highlighting multiple cellular and molecular targets for potential therapeutic development. Nonetheless, contemporary care is primarily characterized by non-pharmacological interventions and symptomatic pharmacological treatments, with a scarcity of strategies that alter fundamental mechanisms. The blood-brain barrier (BBB) is a significant hurdle to overcome - its structure, transport routes, and context-specific dysfunction in ASD both limit and create opportunities for central nervous system (CNS) drug delivery at the same time. In this context, nanomedicine presents novel opportunities and nanoparticles are currently emerging for various neurological applications in preclinical and clinical studies. They can be designed for targeted drug delivery to the brain, for the development of sophisticated ASD models and for diagnostic and theranostic purposes. This review incorporates the clinical manifestations, mechanistic pathways, BBB biology, and nanoparticle-based methodologies to provide a developmentally informed framework for nano-enabled interventions in ASD.

Keywords: autism spectrum disorder, nanomedicine, blood–brain barrier, targeted delivery, gut–brain axis

Introduction

It is frequently asserted that the brain is the most intricate structure in the body. This is due not only to its regulation of thinking, behavior, and emotion, but also to its susceptibility to various neurological and psychiatric illnesses.[1,2] Neuroscience has advanced significantly over recent decades; nonetheless, the treatment of central nervous system (CNS) illnesses remains exceedingly challenging. Both the complexity of the CNS regarding its architecture and function, along with biological protective mechanisms, such as the blood-brain barrier (BBB) which complicate drug penetration and frequently diminish their specificity and safety, are significant hurdles to be overcome.[3]

ASD is a distinct neurodevelopmental disease marked by persistent difficulties in social communication and restricted or repetitive behaviors. Over the past two decades, the worldwide prevalence of ASD has increased markedly. While improved diagnostic awareness substantially influences this tendency, various environmental factors impacting early neurodevelopment have also been investigated. The World Health Organization (WHO, 2021) estimates that roughly 1 in 127 individuals worldwide are on the autism spectrum, representing approximately 0.8% of the global population.[4,5] The Global Burden of Disease (GBD 2021) research validates these findings, revealing an age-standardized prevalence of 0.788% and an incidence rate of 9.3 per 100,000 individuals.[6] Significant regional variance exists. The U.S. Centers for Disease Control and Prevention (CDC, 2024) indicate that approximately 1 in 36 children are affected by the condition; nevertheless, most low- and middle-income countries continue to record lower prevalence rates, albeit with gradual

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increases.[7,8] These disparities are likely attributable to variations in diagnostic practices, healthcare systems efficacies, and public awareness of the issue, rather than genuine biological differences. Nonetheless, the rising incidence of ASD diagnoses globally indicates an urgent need for interventions that can immediately target the fundamental neurological processes of the illness.[9]

Since Leo Kanner's 1943 characterization of ASD,[10] scientific views on ASD have changed. Once thought to merely psychogenic, it is now recognized as a complex condition impacted by genetic, neurological, and environmental factors.[11,12] ASD patients often have comorbidities like epilepsy, anxiety, depression, and ADHD, which complicate diagnosis and treatment.[10] Although behavioral evaluation tools have improved, clinical observation is still the main way to diagnose ASD. Due to individual heterogeneity, no reliable biochemical or neuroimaging biomarkers have been found.[10] Current interventions, such as Early Intensive Behavioral Intervention (EIBI), Applied Behavior Analysis (ABA) speech and occupational therapy, and other behavioral supports, aim to improve communication and daily tasks. Drugs usually address ASD symptoms like irritability and hyperactivity, not the illness itself. Modern treatments rarely address the disorder's neurobiology.[13]

Nanotechnology has attracted considerable attention as a prospective approach in this setting.[2,14] Nanoparticles (NPs) exhibit considerable potential in drug delivery systems. Their diminutive size, customizable surface characteristics, and overall superior biocompatibility render them more effective than conventional delivery systems. They can traverse the BBB more effectively and enhance medication stability, bioavailability, and overall therapeutic efficacy.[15] As a result, nanotechnology-based methods are increasingly being explored for neurological and neurodevelopmental problems, such as Autism Spectrum Disorder (ASD).[16]

This review summarizes ASD knowledge and examines the potential of nanotechnology to diagnose and treat ASD in preclinical studies as of 2026. Interest is in NP-mediated drug delivery systems and nanoscale diagnostic technologies that potentially improve ASD and other neurodevelopmental disorder treatment, and finally pave the way for future clinical studies.

Clinical Manifestations of ASD

ASD is marked by persistent challenges in social communication and interaction, alongside constrained and repetitive behavioral patterns, interests, or activities. The diagnostic framework now encompasses atypical sensory reactivity, including hyper-responsiveness, hypo-responsiveness, or unusual sensory interests, which have been acknowledged as a fundamental aspect of the phenotype. Symptoms generally appear in early development and endure throughout life, although their manifestation and the requisite level of support can vary significantly among individuals.[17] A defining characteristic of ASD is its heterogeneity. Language and cognitive skills cover a wide range, from very low levels of intelligence to very high levels of intelligence or anywhere in between.[2] Motor coordination difficulties and variations in sensory processing are frequently noted and may affect daily functioning in nuanced yet significant manners.[18] ASD seldom manifests as a singular condition. Neurological comorbidities are especially important to note. Epilepsy affects about 2–60% of people with ASD, and this is especially true for those who also have an intellectual disability.[19] This shows that ASD is more than just a problem with social-cognitive circuits; it also affects other neural systems.[20] Systemic conditions are also common such as sleep disturbances, encompassing insomnia, circadian rhythm irregularities, and parasomnias, manifesting at elevated frequencies, and can markedly intensify diurnal behavioral and emotional difficulties. Multiple meta-analyses[20] have shown that autistic children are more likely than non-autistic children to have gastrointestinal problems like constipation, diarrhea, stomach pain, and reflux.[21] Psychiatric comorbidities, such as ADHD, anxiety disorders, and mood disturbances, are also common and frequently lead to significant functional impairment. These multisystem characteristics collectively highlight the necessity for evaluation and intervention strategies that transcend a solely neurocentric paradigm, advocating for a more holistic biopsychosocial approach.[18] Figure 1 demonstrates the clinical manifestations of ASD.

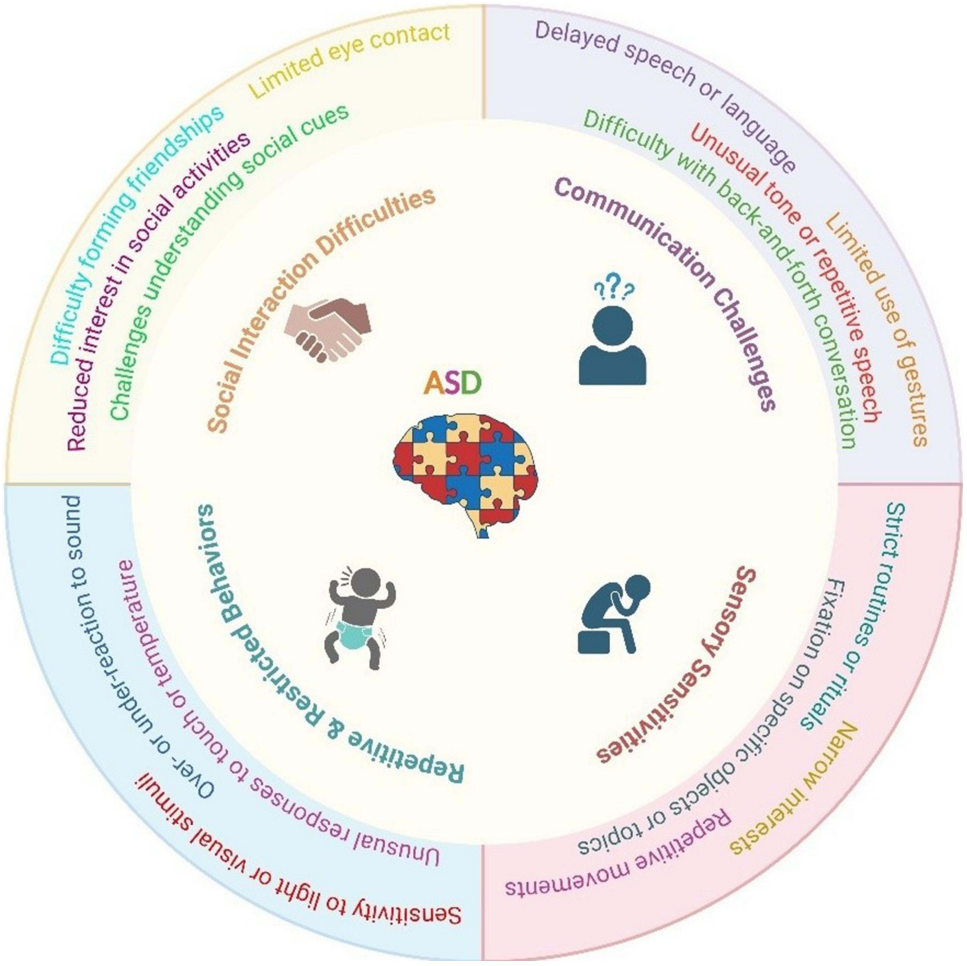

Figure 1 Clinical features of ASD (Created with BioRender.com).

Cellular and Molecular Pathophysiology of ASD: Implications for Nanomedicine Therapeutic Development

ASD originates from disruptions across multiple hierarchical biological levels, including genes, chemical processes, brain circuits, and extended networks. Although the complete causal architecture remains difficult to elucidate, numerous cellular and molecular pathways have been repeatedly associated with it. These pathways are becoming significant for discovering new treatments as they offer distinct biological targets that can potentially be modified through pharmaceuticals, genetics, or nanotechnology. The key mechanistic domains relevant to therapeutic innovation are outlined below.[22,23]

Synaptic Scaffolding and Transmission

Significant evidence suggests that synapse disruption is a fundamental element in ASD. Loss-of-function mutations and copy-number variants impacting synaptic scaffolding and adhesion proteins, particularly within the SHANK, neuroligin (NLGN), and neurexin (NRXN) families, alter the formation of excitatory synapses and reduce synaptic plasticity. These abnormalities undermine the integrity of glutamatergic synapses, affecting both microcircuit stability and long-range connectivity.[24,25] In particular syndromic variations of ASD, namely Phelan–McDermid syndrome caused by SHANK3 haploinsufficiency, preclinical studies suggest that restoring SHANK3 expression can restore synaptic function and reverse core behavioral abnormalities. The results offer compelling evidence for a direct gene → circuit → behavior link and highlight the potential of gene-targeted therapies for specific genetic subgroups.[26,27]

Excitation–Inhibition (E/I) Imbalance

A further significant mechanistic topic pertains to alterations in the equilibrium between excitatory and inhibitory transmission between cortical and subcortical networks. Disruptions in GABAergic interneurons and alterations in glutamatergic transmission leads to network hyperexcitability and atypical oscillatory patterns. Many individuals believe that these issues are the underlying causes of sensory hypersensitivity, motor stereotypes, and repetitive behaviors.[28,29] Whilst pharmacological treatments to restore excitatory/inhibitory balance show theoretical promise; in practice, systemic modulators often have adverse off-target effects. Such difficulties underscore the need for more precise delivery systems that can alter circuit dynamics with less systemic effects.[30]

Maternal Immune Activation and ASD

Maternal immune activation (MIA) is known as one of the causes of ASD. Various researchers indicate that inflammatory processes during pregnancy may enhance the risk of neurodevelopmental disorders in offspring which may trigger the release of pro-inflammatory cytokines that can change the maternal–placental–fetal interface resulting in dysregulation of inflammatory cytokines like interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-17A (IL-17A). Finally, these changes in inflammatory pathways can leads to impaired cortical development and contribute to the emergence of behavioral phenotypes associated with ASD. Furthermore, maternal inflammation may lead to activation of microglia in the developing fetal brain and also lead to disruption of synaptic connectivity which is a key feature in ASD pathophysiology.[31–33]

mTOR/PI3K-AKT Signaling

Hyperactivation of the mTOR pathway has been documented in multiple ASD models and in human genetic variants linked to PTEN, TSC1/2, and associated signaling elements. Excessive mTOR activity disrupts the production of synaptic proteins, the morphology of dendrites, and neuronal development. Modulating mTOR signaling in animal models has shown the ability to rectify synaptic defects and enhance behavioral deficits, suggesting that targeted pathway inhibitors may be effective in ASD subgroups marked by discernible mTOR–PI3K–AKT dysregulation.[34,35]

Neuroinflammation and Immune Dysregulation

The participation of the neuroimmune system constitutes another substantial and reproducible discovery. Research consistently indicates microglial activation, increased levels of pro-inflammatory cytokines (such as IL-6 and TNF-α) and altered peripheral immunological profiles in both human ASD cohorts and animal models. Neuroinflammation can adversely affect synaptic pruning, activity-dependent maturation, and functional connectivity. These results provide a molecular rationale for exploring immune-modulating treatments, including anti-inflammatory drugs, targeted cytokine regulation, and, in experimental contexts, cell-based immunotherapies.[36,37]

Gut–Brain Axis and Metabolism

Increasing evidence indicates a bidirectional influence between the gut microbiome and neurodevelopment.[32,33,38,39] Dysbiosis, in conjunction with alterations in microbial metabolites (such as short-chain fatty acids and tryptophan-derived substances), can influence the development of the CNS, neurotransmitter synthesis, and behavior. Clinical trials, though still limited, suggest improvements in gastrointestinal and behavioral symptoms following therapies that affect the gut microbiome, such as particular probiotics, dietary modifications, and fecal microbiota transplantation (FMT).[33] These findings suggest a viable peripheral-to-CNS treatment route that may improve upon direct neuromodulatory approaches.

ASD Treatment

The therapeutic management of ASD includes both non-pharmacological and pharmaceutical approaches, each customized to address the considerable heterogeneity characteristic of the illness. The main goals of these therapies are to improve adaptive functioning, promote communication and learning, reduce maladaptive or unpleasant behaviors, and eventually enhance the overall quality of life.[25] Treatment strategies are typically customized for each individual, as symptoms vary

among patients, necessitating a collaborative approach including a team of professionals which consider cognitive, behavioral, emotional, and physiological elements to build a comprehensive care plan. Growing data highlight the importance of the microbiota–gut–brain axis in ASD.[40,41] Many autistic children experience gastrointestinal issues correlated with alterations in their gut microbiota composition that can be quantified. These alterations encompass modifications in the bacteroidetes/firmicutes ratio, genus-specific disturbances, and elevated concentrations of microbially produced metabolites, particularly short-chain fatty acids such as propionic acid. Biomarkers reflecting increased intestinal permeability and epithelial injury frequently correlate with the intensity of behavioral symptoms, reinforcing the concept that "leaky gut" physiology may affect symptom expression in specific individuals. Communication along the microbiota–gut–brain axis transpires through multiple mechanisms, including vagal and enteric nervous system signaling, immune and cytokine activity, endocrine modulation, and microbial metabolites that influence central nervous system circuits and the integrity of the BBB. These interconnected circuits offer a medically plausible method via which gut physiology may affect neurodevelopment and behavior. Preliminary clinical investigations provide initial validation for this approach. Research employing tailored probiotics or synbiotics suggests that these therapies may alleviate gastrointestinal symptoms and, in some cases, produce slight improvements in behaviors related to ASD. Nonetheless, considerable heterogeneity in microbial strains, dosage protocols, inclusion criteria, and study design has limited the ability to draw conclusive findings. Cristofori et al emphasize that the next advancements will require biomarker-stratified, adequately powered clinical trials to evaluate precision microbiome manipulation as a potential enhancement to multimodal ASD care.[42]

Non-Pharmacological ASD Treatment

Non-pharmacological therapies remain fundamental, emphasizing evidence-based behavioral, developmental, educational, and physical approaches.[43,44] Behavioral therapies, particularly Applied Behavior Analysis (ABA), Discrete Trial Training (DTT), and Pivotal Response Training (PRT), represent the most rigorously tested methods in contemporary therapeutic practice.[45]

The Lovaas approach is a highly structured, therapist-directed intervention that integrates the principles of ABA and DTT. It focuses on deconstructing complex skills into smaller, educational components to enhance learning in communication, cognition, social interaction, and daily adaptive behaviors, while concurrently reducing maladaptive habits.[46,47] Conversely, PRT is a form of Naturalistic Developmental Behavioral Intervention (NDBI) that emphasizes enhancing intrinsic motivation and fostering spontaneous, child-directed communication. Therapy is included into play and daily activities, connecting educational possibilities with the child's inherent interests and routines. Despite the structural and philosophical differences between ABA/DTT and PRT, both methodologies have demonstrated substantial advancements in various developmental domains, including language acquisition, social engagement, and adaptive functioning. Their complementary strengths underscore the need for individualized treatment planning that aligns intervention tactics with each child's unique behavioral traits, learning preferences, and developmental needs.[48,49] Table 1 and Figure 2 summarize the common interventions in ASD treatment.

Pharmacological Treatments

In addition to non-pharmacological methods, pharmacological treatments are an important part of treating the behavioral, emotional, and physical problems associated with ASD.[54] These medications do not address the fundamental diagnostic characteristics of ASD; instead, they focus on alleviating concomitant symptoms such as irritability, aggression, anxiety, hyperactivity, or sleep disturbances - that can profoundly impact daily functioning and overall health.[55] Table 2 provides a summary of the main drugs that are currently used to treat ASD, along with their uses and other important information.

The BBB in ASD: Alterations and Design Opportunities

BBB Structure and Transport Routes

The BBB is the primary barrier regulating the exchange of chemicals between peripheral circulation and the central nervous system. Its primary characteristic is a highly selective permeability, allowing essential nutrients to enter the brain

Table 1 Non Pharmacological Interventions for ASD

Interventions	Core Principles	Therapeutic Goal	Outcome	Ref
ABA/DTT	Operant-conditioning framework; structured one-on-one sessions breaking complex behaviors into discrete, teachable components.	Improve language, cognitive, and social functioning; reduce maladaptive behaviors.	Significant gains in IQ, communication, and academic readiness, particularly with early intensive programs.	[47,50,51]
PRT	Naturalistic Developmental Behavioral Intervention (NDBI) integrating ABA with developmental psychology; focuses on intrinsic motivation.	Enhance motivation, initiation, and generalization of communication and social skills.	Improves spontaneous communication, social reciprocity, and adaptability across contexts.	[49,52,53]
EIBI	High-intensity extension of ABA delivered 20–40 h/week with strong parental involvement.	Promote early learning and adaptive behavior; reduce stereotype.	Moderate-to-large improvements in communication, adaptive skills, and cognition.	[43,44]
Occupational Therapy (OT)	Sensory-integration and motor-planning framework targeting participation in daily tasks.	Improve fine-motor coordination, sensory processing, and self-care independence	Better sensory regulation and daily-living performance.	[43,44]
Speech and Language Therapy (SLT)	Focuses on receptive/expressive language and social-pragmatic communication.	Enhance speech, literacy, and interaction skills.	Strong evidence for improved language and pragmatic communication.	[43,44]
Social-Skills & Cognitive-Behavioral Therapy (CBT)	Targets social cognition, emotional regulation, and behavioral self-management.	Reduce anxiety; improve peer relationships and coping skills.	Evidence for reduced anxiety and enhanced social functioning.	[43,44]
Physical/Sensory Integration Therapy	Motor-based, vestibular-proprioceptive training.	Improve coordination, balance, and sensory modulation.	Mixed but generally positive effects on motor and sensory outcomes.	[43,44]

while excluding pathogens and poisons. The BBB neurovascular unit maintains vascular stability and neural equilibrium, and comprises of endothelial cells linked by tight junctions, pericytes tightly associated with the endothelial cells, and astrocytic endfeet.[57]

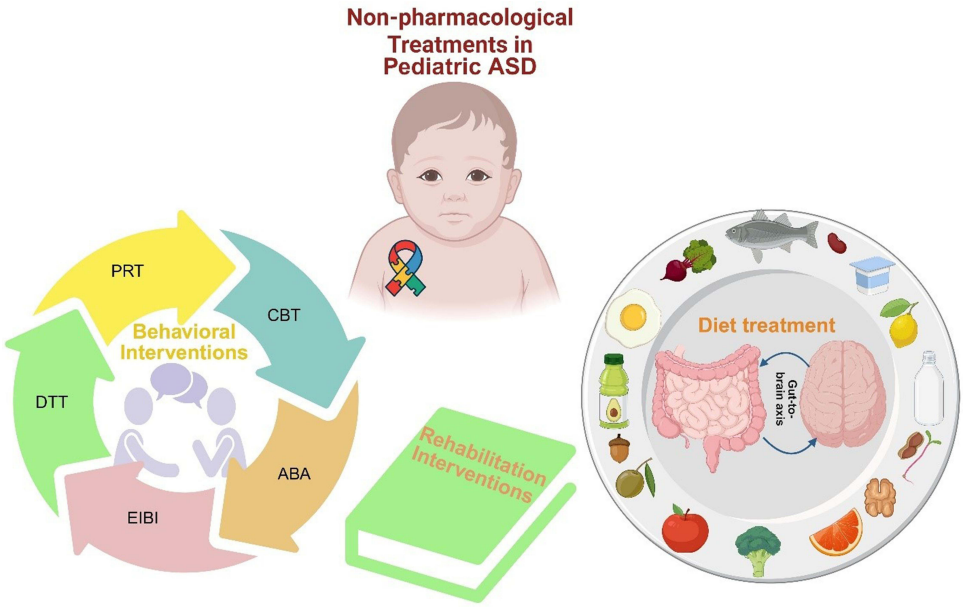

Figure 2 Common intervention strategies for ASD (Created with BioRender.com).
Abbreviations: ABA, Applied Behavior Analysis; CBT, Social-Skills & Cognitive-Behavioral Therapy; DTT, Discrete Trial Training; EIBI, Early Intensive Behavioral Intervention; and PRT, Pivotal Response Training.

Table 2 Principal Pharmacological Interventions for ASD

Drug Class/Representative Agents	Mechanism of Action/ Target Pathway	Therapeutic Indications in ASD	Efficacy and Limitations	Ref
Atypical Antipsychotics (Risperidone, Aripiprazole)	Dopamine D_2 and serotonin 5-HT_2A receptor antagonists	Irritability, aggression, self-injury	The only FDA-approved drugs for ASD; effective for irritability but may cause metabolic and extrapyramidal side effects	[54,56]
Selective Serotonin Reuptake Inhibitors (SSRIs)	Block presynaptic serotonin reuptake, enhancing serotonergic tone	Anxiety, depression, repetitive behaviors	Mixed results; may cause behavioral activation in youth; best for comorbid anxiety	[23,54]
Stimulants/Non-Stimulant ADHD Medications (Methylphenidate, Atomoxetine)	Enhance dopamine/ norepinephrine transmission	Attention-deficit and hyperactivity symptoms	Moderate benefit; possible irritability or appetite loss	[54,56]
Mood Stabilizers/Anticonvulsants (Valproate, Lamotrigine)	GABAergic modulation and reduced neuronal excitability	Epilepsy, mood instability, aggression	Effective for seizures; inconsistent results for core ASD symptoms	[56]
Melatonin and Sleep Modulators	Regulate circadian rhythm; improve sleep onset latency	Sleep disturbances	Safe and effective adjunct for insomnia; enhances overall well-being	[54]
Oxytocin and Vasopressin Analogues (Experimental)	Target social-neuropeptide systems involved in bonding	Social interaction and communication deficits	Early trials show modest effects; dosing and delivery unresolved	[23]
Glutamatergic Modulators (eg, Memantine)	NMDA-receptor modulation, reduces excitotoxicity	Cognitive rigidity and social behavior deficits	Limited but emerging evidence; potential adjunct option	[23]

In the late 1800s, Paul Ehrlich's dye tests showed that certain chemicals in the blood did not color brain tissue. This resulted in the hypothesis of a barrier separating the blood from the brain parenchyma.[58] The selective shielding role remains crucial, as disruption to the BBB can lead to numerous neurological disorders, including inflammatory and viral diseases, meningitis, brain tumors, neurodegenerative syndromes such as Alzheimer's disease, and traumatic brain injury.[59,60] A network of tight junction proteins constitutes a fundamental component of the BBB's architecture. These proteins constrict paracellular channels and maintain the low-permeability milieu characteristic of healthy cerebral vasculature. The effective pore size of healthy tight junctions is around 4 nm;[61] however, when the barrier function is compromised, such as during inflammation or edema, these pores can significantly enlarge, occasionally reaching several hundred nanometers. The pathological BBB has increased permeability, detrimental to neural stability, offering prospects for NP-mediated drug delivery, enabling therapeutic NP medicines to penetrate brain tissue more readily than under normal conditions.[62]

Numerous strictly regulated mechanisms exist for drugs to traverse the BBB. This encompasses passive diffusion of small lipophilic molecules, restricted paracellular movement, carrier-mediated transport of glucose, amino acids, and other vital nutrients, ion-channel activity, adsorption-mediated transcytosis, receptor-mediated transcytosis via ligands such as transferrin or insulin, ATP-dependent efflux systems like P-glycoprotein, and diverse forms of endocytosis.[58]

Small, lipophilic compounds primarily cross the BBB through passive diffusion, enabled by their ability to incorporate into the lipid bilayer of the endothelial cell membrane. The capacity of a substance to diffuse in this manner is primarily influenced by three physicochemical properties: its capacity to establish hydrogen bonds, its molecular size, and its hydrophobic characteristics.[58] Molecules under 500 Da with octanol-water partition coefficients favoring octanol by a factor of around 10^2–10^4 can readily traverse the BBB. Oxygen, carbon dioxide, caffeine, and ethanol exemplify typical substances. Conversely, ions and most tiny hydrophilic solutes can traverse other tissues via paracellular transport; however, the tight junctions of the brain capillaries effectively obstruct this pathway.[58]

Passive diffusion across the BBB relies on two primary transporter types: solute carrier (SLC) transporters and ATP-binding cassette (ABC) transporters. SLC proteins facilitate the transport of substances into and out of the cell, as well as the delivery of essential nutrients such as glucose and amino acids to the brain. Transmembrane proteins constitute ion

channels, facilitating the movement of certain ions across the endothelium membrane.[63] Seven subfamilies of ABC transporters predominantly reside on the luminal surface of BBB endothelial cells. Each transporter contains a transmembrane domain (TMD) and a cytosolic nucleotide-binding domain (NBD). P-glycoprotein (P-gp), encoded by ABCB1, is the most recognized of these. P-glycoprotein is present at several physiological barriers and functions as a potent efflux pump, aggressively eliminating xenobiotics and numerous therapeutic medicines from the central nervous system. The activity of P-glycoprotein presents a significant challenge for pharmaceuticals: even if a medicine penetrates endothelial cells, P-gp can inhibit its accumulation in the brain parenchyma.[64,65] Larger molecules, including most NPs, typically depend on vesicular transport mechanisms to cross the BBB. These pathways include transcytosis, caveolae-mediated endocytosis, receptor-mediated endocytosis, macropinocytosis, and various forms of pinocytosis which are defined as:[66,67]

- Transcytosis is the process by which vesicles move from the luminal membrane to the abluminal membrane (or the other way around) through endothelial cells.[68]
- Caveolae-mediated endocytosis begins in lipid raft microdomains that are rich in caveolin, cholesterol, glycosphingolipids, sphingomyelin, and lipid-anchored glycoproteins. Caveolin (~22 kDa), characterized by cytosolic N- and C-termini, functions as a structural indicator of cellular integrity and is frequently dysregulated in cancer. Caveolae that have been internalized create vesicles that look like flasks. These vesicles then join together to form caveosomes, which then join together with lysosomes.[69]
- Clathrin-mediated endocytosis requires adaptor proteins, membrane receptors, phosphatidylinositol-4,5-bisphosphate (PIP_2), GPCRs, and multiple accessory proteins that coordinate vesicle formation.[70]
- Macropinocytosis, on the other hand, makes big, uneven vesicles that take in fluid and matrix components from outside the cell. Actomyosin dynamics drive this process, and polypeptide growth factors usually speed it up.[71]

Even though these pathways work in many different types of cells, caveolae-mediated uptake, clathrin-coated pits, and micropinocytosis are some of the most important vesicular pathways in BBB endothelial cells. Their relative contributions are important for designing NPs that can deliver drugs to the CNS quickly and accurately.[72]

BBB Dysfunction in ASD

Alterations in the integrity and transport dynamics of the BBB may contribute to the neurobiological variability observed in ASD.[73] Numerous documented issues, such as diminished levels of tight-junction proteins (eg, claudin-5), elevated concentrations of inflammatory mediators, and alterations in transporter expression, align with permeability and transport pathways previously discussed. The loss or impairment of tight junctions can transform the typical nm paracellular barrier into a significantly more porous interface, perhaps expanding to hundreds of nanometers. Although these conditions may temporarily promote the movement of NPs, they also allow the entry of unwanted solutes, microbial byproducts, and inflammatory mediators, hence worsening neuroinflammation and oxidative stress.[74,75] Alterations in solute carrier (SLC) inflow mechanisms, ATP-binding cassette (ABC) efflux transporters, including P-glycoprotein (P-gp/ABCB1), and inflammation-responsive vesicular pathways, such as caveolae- and clathrin-mediated transcytosis, also modify the transendothelial transport of molecules. These alterations can either impede or facilitate the access of medications to the central nervous system, complicating the development of successful therapies. In this setting, BBB malfunction in ASD represents a "double-edged opportunity": increased permeability may facilitate CNS entrance of therapeutic NPs, while also heightening the danger of off-target accumulation, immunological activation, and unpredictable pharmacokinetics.[63,76,77]

Consequently, the rational nanotechnological design for ASD should prioritize ligand-guided transcytosis over passive leakage. To mitigate cytokine-mediated inflammatory responses and protein corona formation, it is essential to tune the dimensions, surface charge, and chemical composition of NPs. Additional strategies to enhance safety and efficacy encompass the application of stealth coatings to circumvent efflux pumps, the engineering of NPs to evade recognition by P-glycoprotein, or the scheduling of doses to align with "windows" of transient permeability during

regulated physiological or therapeutic conditions. However, these advantages must be evaluated meticulously to prevent exacerbating inflammation or damaging the BBB.[78,79]

One recent study by Ueno et al, provides a thorough review of BBB development, structure, and disease, with implications for ASD.[80] The authors clarify the development of the BBB, comprising endothelial cells, pericytes, astrocytes, and basement membranes, via coordinated angiogenesis, cellular differentiation, and postnatal maturation. Cerebral microvascular endothelial cells display distinct features: robust tight and adherens junctions, limited basal pinocytosis, polarized transporter expression, and increased mitochondrial density. Astrocyte and pericyte signaling modulates vascular tone and BBB permeability, enhancing barrier stability.[80]

Additional research highlights a diverse range of BBB disruptors, encompassing genetic variants (eg, APOE4, SOD1, AQP4), oxidative stress, neuroinflammation, traumatic or hypoxic injury, and alterations in the gut and oral microbiome, which undermine tight junctions, dysregulate transporters, and potentially trigger microbleeds. The breakdown of the BBB appears to precede neuronal dysfunction or degeneration in multiple illnesses, including ASD, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS).[81]

Therapeutic approaches to address BBB dysfunction encompass neurosurgical delivery methods, chemical regulation of permeability, receptor-mediated "Trojan horse" systems, NP and exosome-based drug carriers, microbiome-targeted therapies, and stem cell techniques. Each possesses potential, yet, they must navigate trade-offs concerning specificity, safety, scalability, and translatability. The convergence of BBB processes in neurodevelopmental and neurodegenerative illnesses suggests the possibility of shared, biomarker-driven treatment methods, dependent on rigorous translational validation in future research.[82,83]

Nanoparticles (NPs) in ASD

NPs are materials that have at least one dimension between 1 and 100 nm and can be carefully designed to interact with biological systems at the molecular and cellular levels because they have a high surface-area-to-volume ratio, a tunable shape, and a surface chemistry that can be changed.[84] These traits make it possible to control drug loading, deliver drugs to specific areas, make poorly bioavailable compounds more soluble, and improve pharmacokinetic behavior. In biomedical science, NPs include a wide range of platforms, such as polymeric NPs, liposomes, solid-lipid NPs, gold and magnetic nanostructures, dendrimers, and biomimetic or cell-membrane–coated vesicles. Each of these has its own benefits for use in therapy, diagnosis, and biosensing. NPs have become a revolutionary technology in modern drug delivery and neurotherapeutic research because they can cross physiological barriers, such as the BBB, and deliver active agents in a targeted, long-lasting, or stimulus-responsive way.[85] In this article, we briefly talk about some of their new uses in ASD. The main focus is on how NPs can be used in drug-delivery systems, but we also mention other uses like biosensing and diagnostic platforms. Figure 3 depicts various applications of nanotechnology in ASD.

NP-Based Drug Delivery in ASD

A growing body of research demonstrates that nanocarriers can effectively deliver antioxidants, anti-inflammatory agents, neurotransmitter modulators, and gene-regulatory therapies, showing improved stability, bioavailability, and brain penetration.[86] These methods are particularly advantageous for ASD[87] since they circumvent significant challenges that diminish the efficacy of conventional small-molecule and biologic therapies, including inadequate solubility, rapid systemic clearance, and restricted transport across the BBB.[88]

Advancement by Lv et al involves microglia-targeted nanoformulated bumetanide. Bumetanide, an NKCC1 inhibitor, has produced variable outcomes in clinical trials; nevertheless, NP encapsulation may improve its therapeutic efficacy. They exhibited that PEG–PLA NPs administered into the medial prefrontal cortex (mPFC) of BTBR mice specifically modulated microglial reactivity and restored social novelty preference. The findings suggest that directing NPs precisely to microglia may rectify the limitations of systemic delivery and enhance the precision of existing ASD therapies.[89]

Nanocarriers composed of phytochemicals are increasingly gaining popularity. Naringenin and curcumin exemplify substances possessing antioxidant, anti-inflammatory, and neuroprotective properties. Nevertheless, when administered in free form, they exhibit poor solubility and rapidly degrade. Encapsulating NPs significantly enhances their pharmacokinetic characteristics. BBB entrance and concentration in the brain is an important factor for a NP in ASD treatment. As mentioned above, there are various routes for NP delivery via the BBB and dependent on their characteristics, NPs can

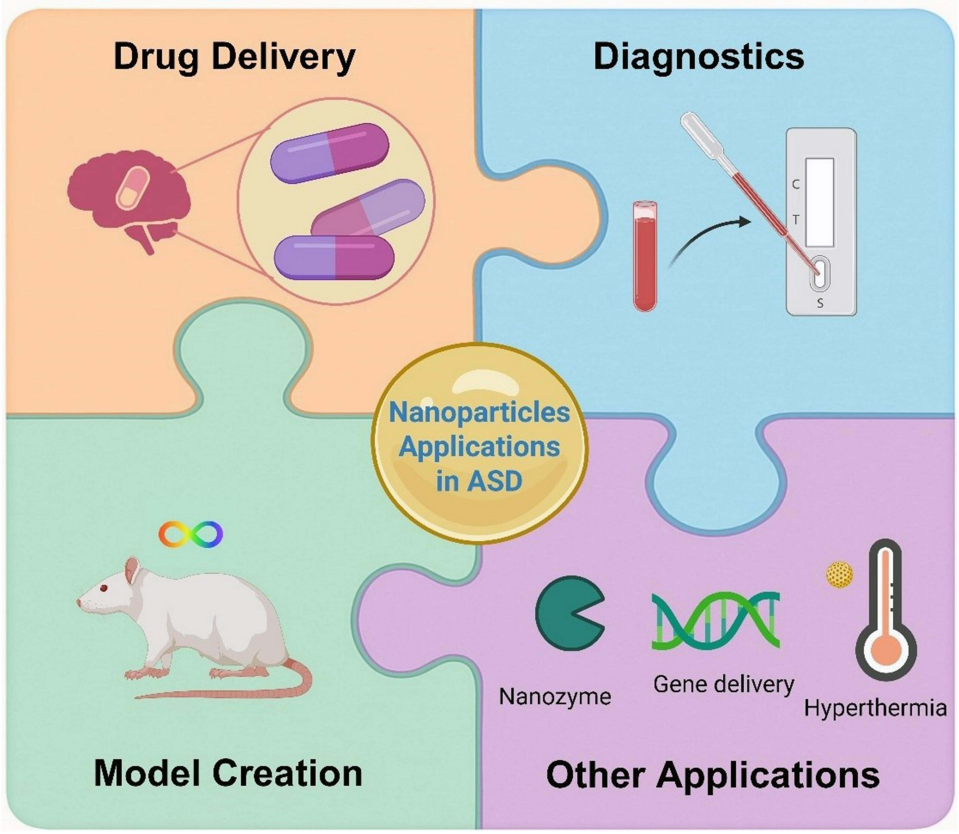

Figure 3 Applications of nanotechnology in ASD (Created with BioRender.com).

use single or multiple approaches. However, the BBB transfer for pharmaceutical agents or macromolecules is extraordinarily meager - as low as just 1% of CNS drugs (out of 7000) can be transferred via the BBB and concentrate in the brain.[90] Other research indicated that less than 5% of CNS-targeted candidate drugs progress from preclinical to clinical stage, because of in adequate brain penetration.[91] Therefore, encapsulating a pharmaceutical agent within nanoplatforms leads to higher BBB entrance resulting in better efficiency.[58] Scientists are designing various NP structures to improve their BBB entrance.[88] For example, Chen et al designed a SPIO NP coated with PEG and insulin that were transferred via the BBB by 24.47% via intraperitoneal injection.[92] In another study, it was observed that 60% of DNAzyme-loaded nanoliposomes with a median size of 68 nm were transferred via the BBB of female BALB/c mice (healthy model) via intravenous administration.[93] Another investigation by Ohta et al revealed that the size of holes created via external energy in the BBB were about 15–120 nm in ICR mice.[94] These improvements developed position NP-mediated drug delivery as one of the most rapidly evolving and mechanistically innovative domains for ASD treatment. Despite being in its nascent phase, the integration of improved BBB permeability, precise administration, and biological specificity highlights nanomedicine as a crucial frontier for the development of future treatments for ASD. Table 3 provides critical studies on using NPs for enhanced drug delivery for ASD.

Nanoparticles as Tools for ASD Model Creation

Growing evidence suggests that NPs can influence neurodevelopmental pathways, leading to behavioral and biochemical alterations linked to ASD and ADHD.[109–111] Besides their therapeutic use, NPs are emerging as experimental instruments for developing environmental, epigenetic, and transgenerational models of ASD.[112,113] Ishido et al developed a silver NP (AgNP)-primed hyperactivity model, which is among the most intriguing findings today. In their study, pregnant mothers received a single oral dose of AgNPs on gestational day 7. For four successive generations, offspring were selectively bred for increased spontaneous motor activity levels. In the fourth generation, AgNP-primed rats exhibited a 1.8-fold

Table 3 Studies on NPs for Drug Delivery for ASD

NPs	In vitro Assays/Results	In vivo Assays/Results	
Prussian Blue nanocatalyst NPs	SH-SY5Y cells (human neuroblastoma cells), lower apoptotic markers and pro-inflammatory cytokines while increasing Bcl-2 and anti-inflammatory signals	Sprague–Dawley rats; improved social interaction, reduced anxiety-like behavior, and enhanced learning and memory	[95]
Gold NPs	NA	Wistar rats, oral 2.5 mg/kg for 1 week; increased antioxidant defenses, preserved glutathione, and improved plasma antioxidant capacity	[96]
Sumac and gallic acid-loaded nanophytosomes	NA	Wistar rats, oral 20 mg/kg for 4 weeks; improved recognition memory and increased GPx, GRx, SOD, CAT, GSH, TAC, and Nrf2/Keap1 expression in the hippocampus	[97]
Aspirin-PEG-PCL NPs	bEnd.3 and BV2 cells, decrease mitochondrial oxidative stress, DNA injury, and microglial inflammation	ASD model mice, IV 50 mg/kg; improved social interaction, reduced repetitive behavior, and lowered anxiety	[98]
Naringenin loaded poly (lactic-co-glycolic acid) (PLGA) NPs	NA	Sprague–Dawley rats, oral 25 mg/kg for 29 days; ameliorated behavioral and biochemical abnormalities associated with ASD	[99]
Dextran iron oxide NPs	Less macrophage uptake	-	[100]
Nanoemulsions with cannabidiol	NA	Rats. Oral, twice daily at 1–2 mg/animal for 30 days; reduced valproic acid–induced neuronal death	[101]
Erythropoietin loaded in SLN	NA	Wistar rats, 1000–2000 U/kg on days 1–5; improved ASD-like phenotypes and demonstrated hippocampal neuroprotection	[102]
Bumetanide loaded in (PEG-PLA) NPs	NA	C57BL/6 mice, i.p. 10 mg/kg for 7 days; improved repetitive grooming behavior	[89]
Sumac nano-phytosome		Rats, oral 40 mg/kg for 4 weeks; improved memory and increased GPx, GRx, CAT, and TAC	[103]
Magnesium oxide NPs	NA	Wistar rats, i.p. 2.5–5 mg/kg on postnatal days 31–35; improved anxiety and social interaction, induced analgesia, and reduced hyperactivity	[104]
Nanocrystals of Hesperetin	NA	Wistar rats, oral 20 mg/kg/day until end of lactation; improved behavioral deficits and reduced brain oxidative stress and plasma inflammation	[105]
Vitamin D3-Loaded nanoemulsions	NA	Rats, oral 1800 IU/kg daily for 3 months; improved pharmacokinetics, with calcium, oxidative stress, and apoptosis markers remaining normal, indicating NP safety	[106]
Superparamagnetic iron oxide (SPIO) NPs	SH-SY5Y, MTT results showed no significant adverse effect on cell viability	Wistar rats, 15 mg/mL for 30 days, intracerebroventricular infusion for 14 days; improved dendritic spine density in hippocampal CA1	[107]
Thymoquinone-loaded hexosomal lipid/ polymer nanovesicles	NA	C57BL/6J mice, i.p. 10 mg/kg for 21 days; restored anxiety levels, reduced hyperactivity, and lowered malondialdehyde (oxidative stress) levels	[87]
Rapamycin loaded red blood cell membrane	SH-SY5Y, effectively induce autophagy, lower ROS, enhance mitochondrial function, and consequently lower neuronal injury	Sprague-Dawley rats, IV 5 mg/kg for 14 days; activated autophagy, reduced oxidative stress, and preserved mitochondrial function	[108]

increase in hyperactivity, indicating that a single prenatal exposure was sufficient to induce a persistent, heritable alteration in behavior. Conversely, early postnatal injection of valproic acid (VPA) - a conventional neurodevelopmental model of ASD/ADHD - resulted in a similar but less dramatic phenotype (1.4-fold increase in hyperactivity). Genome-wide DNA methylation analysis revealed convergent epigenetic patterns in the mesencephalon of hyperactive rats primed with AgNPs and treated with VPA. The fingerprints encompassed genes critical for neural maturation, synaptic function, transcriptional control, ubiquitination, DNA binding, and histone modification. Examples include Pax6 and Mecp2. The

analogous epigenomic patterns suggest that NPs may act as environmental toxicants inducing ASD- and ADHD-like behaviors, as well as tools for modeling transgenerational, epigenetically mediated neurobehavioral syndromes - an investigative avenue that offers unique opportunities to examine heritable mechanisms in neurodevelopmental disorders.[113]

Another pertinent example is the research conducted by Notter et al which investigated whether prenatal exposure to titanium dioxide NPs (TiO_2 NPs) alters brain development in mice.[112] On gestational day 9, a critical period for fetal brain development, expectant dams received a single intravenous injection of either low-dose or high-dose TiO_2 NPs. The progeny displayed dose-dependent behavioral abnormalities, marked by reduced neonatal ultrasonic vocalizations, compromised juvenile sociability, and heightened prepulse inhibition. These findings indicate essential and interconnected traits of ASD - difficulties in early communication, altered social behavior, and impairments in sensory-motor gating.[112]

The researchers observed no indications of maternal toxicity, complications during pregnancy, or significant fetal deformities. This indicates that TiO_2 NPs may subtly disrupt neurodevelopment in manners that conventional teratological assessments cannot detect. This study provides substantial preliminary evidence that NPs often employed in consumer, industrial, and biomedical contexts may influence neurodevelopment and create environmentally linked ASD phenotypes.[112] Moreover, TiO_2 NPs offer a controlled and reproducible experimental paradigm for examining the impact of ambient nanomaterials on the risk of ASD.[112] These findings collectively demonstrate that NPs can operate as model-inducing agents, enabling the exploration of environmental, epigenetic, and transgenerational factors affecting neurodevelopmental diseases. This dual function - therapeutic and pathogenic - underscores the imperative of rigorously assessing NP safety while harnessing their mechanistic promise for model advancement.[112,113]

NPs in ASD Diagnostics

Besides their therapeutic applications, NPs are increasingly significant in the development of advanced biosensing platforms for ASD. Their unique electrical, optical, and catalytic properties enable the precise detection of molecular biomarkers, advancing ASD assessment towards more objective, rapid, and physiologically pertinent methods. Nanomaterials (such as gold NPs, silicon nanowires, metal-organic frameworks (MOFs), and various carbon-based nanostructures) have proven highly beneficial due to their capacity to enhance signal amplification, improve surface-to-volume ratios, and significantly reduce detection limits.[114]

These nano-enabled biosensors have been employed to measure several biomarkers associated with ASD, including microRNAs (eg, miR-23a-3p, miR-146a, miR-132), inflammatory cytokines, and peptide markers such as β-casomorphin-7.[115,116] Photoelectrochemical platforms utilizing gold NPs included in two-dimensional MOFs enable the detection of microRNAs associated with ASD without the need for labels. Likewise, silicon-on-insulator (SOI) nanowire devices enable the real-time measurement of circulating miRNA profiles associated with neurodevelopmental diseases.[117,118] These technologies collectively potentially facilitate the identification of biomarkers with few or no adverse effects, enable early detection, and monitor the efficacy of treatments for each individual.[117,118]

Ivanov et al developed an ultrasensitive silicon-on-insulator nanowire nanosensor (SOI-NS) for the detection of microRNAs in ASD.[119] The device comprises a CMOS-compatible array of nanowire sensing elements fabricated by gas-phase etching and sophisticated nanolithography techniques. Subsequently, sequence-specific oligonucleotide probes were introduced to facilitate their functionality. The authors employed this approach to directly quantify microRNAs associated with ASD from human plasma. The application of synthetic miRNA analogues in a buffer yielded an exceptionally low detection limit of 10^{-17} M. This research demonstrates that nanostructured semiconductor sensors can detect biomarkers with great precision and without the necessity for labeling. This represents a viable avenue for objective ASD diagnostics.[119] Alosaimi et al developed an environmentally sustainable fluorescent nanosensing probe for the quantification of atomoxetine, a medication commonly utilized to alleviate ADHD symptoms in individuals with ASD.[120] This serves as an additional exemplary instance. The researchers synthesized carbon quantum dots (CQDs) from black-eyed pea beans and subsequently included an atomoxetine–tetraphenylborate combination. The resultant nanoprobe enabled rapid and highly specific detection of atomoxetine through fluorescence quenching in both pharmaceutical

formulations and human plasma. The platform demonstrated exceptional analytical performance, according to all ICH validation standards, and was utilized in a pharmacokinetic study including autistic children with ADHD. This research highlights the therapeutic relevance of carbon-based nanomaterials as sensitive, sustainable, and scalable sensors for drug monitoring in neurodevelopmental care. These advancements indicate that NP-based diagnostics could improve behavioral evaluation, enabling earlier identification, biological stratification, and individualized monitoring of ASD.[120]

Other Nanotechnology Applications in ASD

NP systems have been adapted for gene-regulatory therapies, including siRNA- and microRNA-based approaches. Polymeric and lipid NPs can facilitate the delivery of nucleic acids to dysregulated pathways such as SHANK3 and MECP2; these applications remain predominantly experimental[121,122] however they do introduce a non-viral, ultrasound-facilitated BDNF gene delivery method in a valproic acid (VPA) rat model of ASD. Shen et al designed brain-derived neurotrophic factor plasmid-loaded cationic microbubbles (BDNFp-CMBs), showcasing their significant plasmid loading efficiency and adequate in vivo durability. CMBs exhibited an average particle size of 1.33 ± 0.24 μm with a surface zeta potential of 29.8 mV. During treatment, BDNFp-CMBs were administered intravenously, while focused ultrasound (FUS) was applied transcranially to the prefrontal cortex (PFC) to transiently disrupt the BBB and facilitate local plasmid uptake (sonoporation). Ultrasound in combination with lipid microbubbles effectively and non-invasively opened the BBB, enabling enhanced delivery of BDNF to the brain. Evans blue staining revealed BBB disruption in the ultrasound-irradiated prefrontal cortex, while non-sonicated regions showed no staining. Consistently, fluorescence imaging demonstrated strong signals only in ultrasound-treated areas, confirming localized BBB opening. This technique enhanced BDNF production in the PFC, improved stereotyped, exploratory, and social behaviors, and partially restored neuronal morphology and synaptic ultrastructure upon electron microscopy compared to untreated VPA mice.[123]

Furthermore, nanomedicine establishes a conceptual connection between the beneficial effects of fever/hyperthermia on ASD symptoms and targeted, controllable therapies. Clinical and preclinical evidence suggests that temporary elevations in body or brain temperature may briefly improve social behavior and reduce repetitive symptoms in individuals or animal models with ASD, likely by influencing neuroinflammation, synaptic function, and neuromodulatory systems.[124,125] Magnetically responsive or thermosensitive nanocarriers may replicate this "fever-like" condition in a spatially and temporally regulated manner - either by inducing mild, localized hyperthermia in specific brain regions or by associating heat generation with the controlled release and solubility enhancement of ASD-relevant pharmaceuticals.[124] Ansari et al demonstrated that superparamagnetic nanoparticles can generate localized heat under an alternating magnetic field to induce in situ drug amorphization within oral solid dosage forms, thereby enhancing drug dissolution and bioavailability without compromising dosage form integrity. TEM analysis with log-normal distribution fitting revealed primary particle sizes of 17.6 nm and 17.3 nm for zinc ferrite and manganese ferrite nanoparticles, respectively, indicating a narrow size distribution suitable for effective magnetic hyperthermia.[124]

Additionally, nanozymes (that is, catalytic nanomaterials with enzyme-mimetic antioxidant capabilities) have been studied for their ability to alleviate oxidative stress and neuroinflammation, both acknowledged contributors to the pathogenesis of ASD. A restricted but growing body of research has examined NP-mediated hyperthermia and photothermal therapy, particularly gold and carbon nanomaterials, as potential regulators of neuroinflammatory responses; nonetheless, these approaches remain predominantly experimental concerning neurodevelopmental disorders. These exploratory applications illustrate the considerable therapeutic and mechanistic potential of nanotechnology in ASD research; nonetheless, most remain in the conceptual or early preclinical stages and require substantial validation before clinical application.[126,127] Feng et al reported the development of a calcium hexacyanoferrate (III) (CaH) nanocatalyst designed to restore redox homeostasis as a therapeutic strategy for autism spectrum disorder. The study demonstrated that CaH nanocrystals effectively regulated oxidative stress and neuroinflammation, leading to a significant improvement in neurobehavioral outcomes. TEM images revealed the near-spherical morphology of CaH nanocrystals with an average size of 2.6 nm, while zeta potential measurements showed values of −9.4 mV in water, −21.0 mV in phosphate-buffered saline, and −9.8 mV in Dulbecco's modified Eagle medium, indicating medium-dependent surface charge behavior and good colloidal stability.[127]

Gong et al present a detailed example by engineering Prussian blue NPs (PB NPs) to serve as multi-enzyme-mimetic nanozymes for ASD therapy. These PB NPs are designed to function as superoxide dismutase, glutathione peroxidase, catalase, and peroxidase, rendering them broad-spectrum antioxidants in the brain. In preclinical ASD models, systemic injection of PB NPs leads to substantial scavenging of reactive oxygen species and the re-establishment of redox equilibrium. TEM images showed that Prussian blue nanoparticles (PB NPs) exhibited a cubic morphology with an average size of approximately 30 nm. Confocal laser scanning microscopy (CLSM) following live/dead staining confirmed that PB NPs effectively preserved cell viability. Furthermore, flow cytometry analysis demonstrated that PB NP treatment markedly reduced apoptosis induced by H_2O_2 and VPA, with apoptosis rates decreasing from 26.3% to 10.9% and from 24.5% to 7.3%, respectively.[95] This molecular alteration is evidenced by the diminished activation of apoptotic markers, such as cleaved caspase-3 and Bcl-2–associated X protein, along with an elevation in the anti-apoptotic protein Bcl-2. Simultaneously, PB NPs mitigate neuroinflammation by decreasing pro-inflammatory cytokines and increasing anti-inflammatory cytokines, so preventing glial overactivation. These synergistic antioxidant, anti-apoptotic, and anti-inflammatory properties enhance social interaction, reduce anxiety-like behavior, and elevate cognitive performance in ASD-like animals, illustrating the therapeutic potential of nanozymes in recalibrating oxidative and inflammatory pathways associated with ASD pathology.[95]

Toxicity Issues of NPs

Paying attention to NP distribution and their side effects are essential matters when designing a nanoplatform. Nanoplatforms can induce toxicity issues due to their interactions within other cellular structures and also because of their loaded agent.[128] Various factors determine NP toxicity such as mean diameter, zeta potential, use of targeting agents and their components.[129] To clearly define nanoformulation safety, various steps should be completed which are the same as ones for drug screening and to make them ready for commercialization. According to the regulatory guidelines for drug screening, ADME (Absorption, Distribution, Metabolism, and Excretion) and QSAR (Quantitative Structure–Activity Relationship) should be performed followed by in vitro cytotoxicity assays and preclinical examination. After complete fulfilment of preclinical assays from acute to chronic trials, clinical trials can be started.[130,131] It is stated that NP toxicity management contains eight steps including: foundation of safety issues just for the nanoformulation, identification of NPs with biological moiety interactions, identification of their permeability within barriers such as the BBB, accurate dose escalation of NPs, determining standards for NP bio-fate, extension of data regarding NP biodistribution, determination of international standards, and modification of regulatory issues.[129]

Clinical Trials and Future Directions

To date in 2026, NP-based therapies for ASD have had limited applications in clinical environments. One recent comprehensive analysis concluded that "there is currently no established nanomedicine treatment specifically designed for ASD".[132] An examination of prominent clinical-trial registries identified a study concerning a nano-encapsulated probiotic formulation (K11-TMAX) intended to mitigate gut-brain axis inflammation in children with ASD (ClinicalTrials.gov identifier NCT06382909); nonetheless, this intervention is categorized as a nutraceutical rather than a brain-targeted nanotherapeutic. This was a randomized, double-blind Phase III clinical trial (NCT06382909) evaluating a probiotic-based, partly nano-encapsulated intervention in children aged 3 to 11 years with ASD. The researchers analyzed three groups: (1) a placebo, (2) K11-T probiotic alone, and (3) K11-Tmax, which is the same probiotic supplemented with amino acids, fatty acids, and vitamins. The primary objective was to evaluate whether K11-T and K11-Tmax improve neuropsychiatric, sociopedagogical, and inflammatory outcomes in ASD.

Sociodemographic and clinical characteristics characterized the children, thereafter assessed using three validated scales: Vineland-3 (adaptive behavior; parent report), ADOS (core autistic symptoms; clinician evaluation), and CARS (severity; teacher report). The study concurrently assessed serum biomarkers (insulin, C-reactive protein, prolactin, cortisol) and fecal calprotectin to examine inflammatory and metabolic impacts. Finally, it evaluated the impact of the enhanced K11-Tmax formulation on behavior, cognition, education, and inflammation in comparison to K11-T alone. This suggested gut-brain-microbiota manipulation as a potential supplementary approach for controlling ASD.

Unfortunately, no further registered trials have been located for NPs particularly designed for drug transport across the BBB, nano-enabled imaging, or nano-therapies in ASD populations. This highlights a significant disparity between

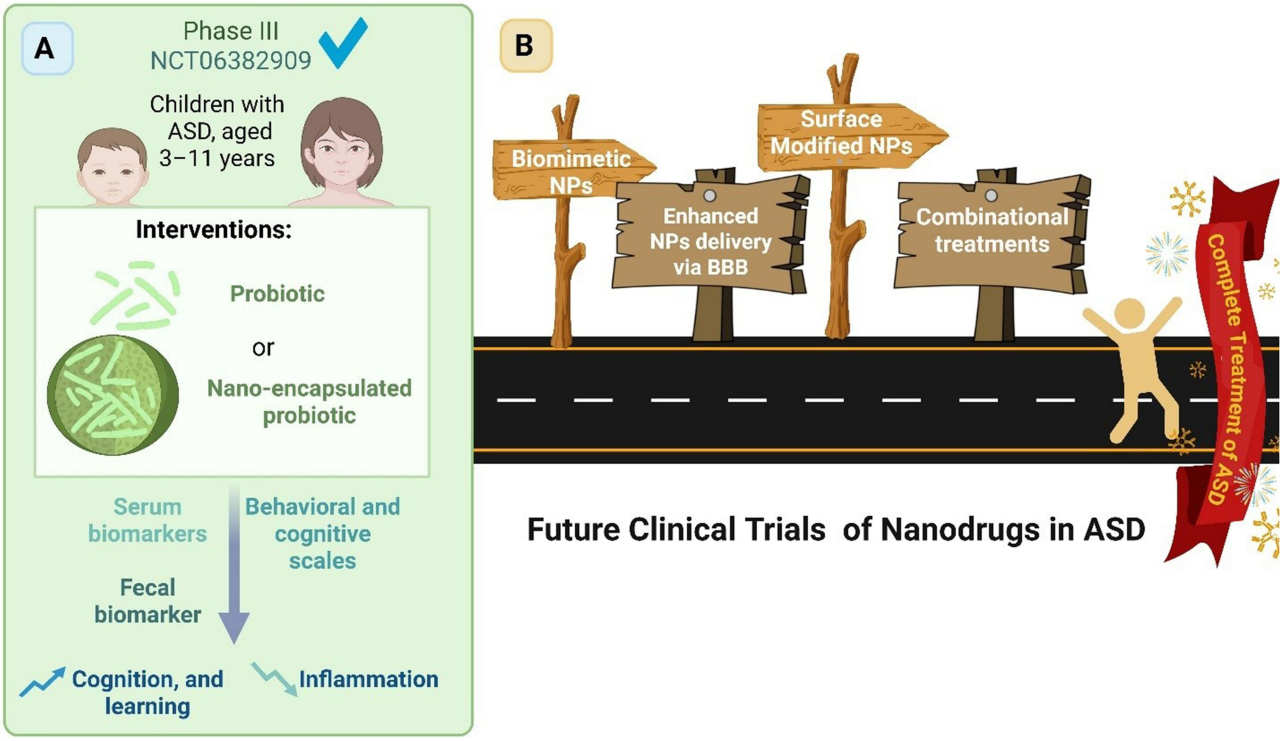

Figure 4 Clinical trials of ASD. (**A**) The completed Phase III clinical trial, including the criteria and nanoformulation applied. (**B**) Future perspectives on the use of innovative nanodrugs in ASD.

promising preclinical research and human studies, indicating the necessity for rigorous clinical trials to ascertain the safety, efficacy, and feasibility of NP-based methods for individuals with ASD.[132]

Future advances in nanotechnology may enable more effective therapeutic strategies for ASD, particularly through the development of combinational NP-based drug delivery systems that address the disorder's multifactorial pathophysiology. By co-delivering multiple therapeutic agents, nanocarriers may simultaneously modulate neuroinflammation, synaptic dysfunction, and immune dysregulation, thereby improving treatment outcomes compared with conventional monotherapies.[133] Moreover, the design of more sophisticated nanoparticles, including surface-modified and multifunctional platforms, holds promise for enhancing BBB penetration targeting specific neural or immune cell populations, and achieving controlled drug release within the brain microenvironment.[134] Although these approaches remain largely preclinical, rigorous safety assessments, standardized characterization, and well-designed clinical trials will be essential to translate advanced nanomedicine strategies into effective and personalized therapies for ASD.[135] Figure 4 shows the completed Phase III clinical trial for ASD, highlighting the applied nanoformulation and eligibility criteria, as well as future perspectives on the use of innovative nanodrug-based strategies in ASD.

Conclusions

ASD is a multifactorial neurodevelopmental condition involving dysregulation of molecular signaling pathways, synaptic function, immune responses, and large-scale brain connectivity, for which current therapeutic strategies remain largely limited to symptomatic management. Nanomedicine expresses a promising approach in ASD treatment, diagnosis and model creation. Nanoparticles enable the rational design of advanced formulations with enhanced stability, controlled release profiles, and improved penetration across the BBB, thereby increasing therapeutic efficacy while minimizing systemic adverse effects. However, despite encouraging preclinical outcomes, the clinical translation of NP-based therapies for ASD remains limited, highlighting a substantial gap between experimental research and human studies. Addressing this gap will require rigorously designed clinical trials to establish safety, efficacy, and feasibility, as well as continued interdisciplinary collaboration integrating nanotechnology, neuroscience, and clinical research. Collectively,

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these efforts may enable nanomedicine-based strategies to advance ASD treatment beyond symptom control toward mechanism-driven and personalized therapeutic interventions.

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Disclosure

The authors declare no competing interest.

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