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Nanoparticle-Mediated Neurotherapeutics: Elucidating Molecular Signaling Pathways and Target-Specific Drug Delivery Mechanisms

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ABSTRACT

The prevalence of neurodegenerative diseases continues to increase with the global population ageing; the blood-brain barrier (BBB) only allows about 98% of small molecule drugs to cross into the central nervous system (CNS) and almost all large molecule biologics are excluded. Traditional small molecule pharmacotherapy can only modulate symptoms. There is some evidence that these nanodrug delivery systems are capable of crossing the BBB and thus could be used as a means to target disease pathways, such as ligand-engineered polymeric, lipid and inorganic nanoparticles, as well as naturally secreted extracellular vesicles, most of which are derived from rodent models. The review here combines what is known about the molecular mechanisms for passage across or around the BBB; it summarizes representative disease-specific approaches to the BBB in Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS); and critically summarizes the molecular mechanisms and the translational hurdles, with the specific goal to distinguish between mechanisms that are known and those that are only observed in the preclinical setting, while clarifying the road to clinical investigation. Limitations include only focusing on systems for which mechanistic and delivery data are available, and the field is moving at a rapid pace so conclusions cannot be drawn from the existing preclinical literature regarding clinical efficacy. However, it nevertheless offers useful information for studies in this area.

Introduction

Neurotherapeutic delivery requires a pharmacologically active molecule to reach the correct anatomical region, enter the relevant cell, and act within an appropriate intracellular compartment. Nanoparticles can influence each of these steps, but evidence that a formulation accumulates in a brain specimen does not establish that its payload reaches a neuronal target. The central argument of this review is that delivery and molecular action must be evaluated as linked, separately testable processes. Otherwise, a favorable imaging result can be mistaken for successful treatment.

The BBB contributes to this problem through specialized endothelial junctions and restricted transcellular trafficking. In experimental systems, MFSD2A is important for BBB formation and function, while lipid transport associated with MFSD2A suppresses caveolae-mediated transcytosis. These findings show that the barrier is an actively regulated cellular phenotype, not simply a passive filter. Engineering a particle to bind an endothelial receptor therefore creates an opportunity for uptake, but does not guarantee productive passage to the abluminal side.

Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and ALS present overlapping problems involving protein handling, neuronal vulnerability, and inflammatory responses, yet their therapeutic targets differ. MS is included as an immune-mediated demyelinating disease with neurodegenerative components, rather than being treated as biologically interchangeable with those disorders. In particular, peripheral immune tolerance may be therapeutically relevant in MS without requiring substantial nanoparticle entry into brain tissue.

The therapeutic background also requires precision. The phase 3 lecanemab trial demonstrated less decline in early, amyloid-confirmed AD over 18 months, while the siponimod EXPAND study examined disability progression in secondary progressive MS. These results make an exclusively symptomatic description of existing treatment inaccurate. They do not remove the need for improved delivery, nor do they establish superiority of a nanocarrier. A new formulation must show an advantage over an appropriate contemporary comparator.

This review pursued three objectives: to explain the mechanisms linking nanoparticle design to BBB transit and intracellular delivery; to evaluate disease-specific molecular interventions across the five conditions; and to identify the evidence needed to translate a delivery signal into a credible clinical development program. The emphasis is on mechanistic interpretation rather than ranking heterogeneous formulations by their largest reported treatment effect.

Review approach and evidence interpretation

This article is a focused narrative review, not an original laboratory investigation or a systematic review. Targeted web searches of indexed biomedical literature and publisher records were conducted on 22 November 2026 using combinations of nanoparticle, blood–brain barrier, transcytosis, transferrin receptor, LRP1, extracellular vesicle, endosomal escape, and the five disease names. Searches also addressed protein corona, lysosomal acidification, antigen-specific tolerance, focused ultrasound, and human clinical outcomes. Recent studies were considered alongside earlier primary experiments that remain informative for delivery mechanisms. Bibliographic identifiers were checked against publisher, PubMed, or DOI registration records.

Priority was given to primary studies reporting a defined material, route of administration, biological model, and delivery or pharmacodynamic endpoint. Studies confined to cultured cells were used for intracellular mechanisms and were not counted as evidence of BBB transit. Non-neurodegenerative models were included only where they clarified a transport mechanism. Molecular antibody shuttles, focused ultrasound, and conventional pharmacotherapies provide context; they are identified separately from nanoparticle formulations. Viral vectors are outside the core synthesis. EV terminology and reporting were considered in relation to MISEV2023, and material reporting in relation to MIRIBEL.

The synthesis distinguishes four questions: where a carrier goes, where active cargo becomes available, whether a molecular target changes, and whether the change improves a relevant outcome. These are interpretive categories, not a validated grading instrument. No duplicate screening, exhaustive database export, formal risk-of-bias score, or meta-analysis was performed. No screening totals or pooled effect estimates are claimed. The numerical figures replot selected published results; they contain no simulated animals, patients, or treatment responses.

Nanocarrier architecture and therapeutic function

Polymeric nanoparticles offer control over composition, ligand presentation, degradation, and release. PLGA can function as a conventional drug carrier, but acidic PLGA nanoparticles have also been investigated as active materials that modify lysosomal pH. This distinction changes the control groups required: an unloaded particle may itself have biological activity. Comparing a loaded formulation only with untreated disease can therefore confound carrier activity with payload delivery.

Lipid nanoparticles and liposomes can accommodate nucleic acids, peptides, and small molecules, but their performance depends on more than encapsulation. Changes in lipid composition can redirect functional RNA delivery among peripheral organs, as shown by selective organ targeting experiments. Those results demonstrate the importance of formulation chemistry, not generic BBB permeability. A liver- or lung-directed lipid composition cannot be assumed to confer brain targeting.

Inorganic materials can act as carriers, imaging agents, or therapeutics. Gold nanoparticles facilitate elemental measurement of tissue distribution, whereas catalytic gold nanocrystals have been studied as active neurotherapeutics. These are materially and pharmacologically different products. Benefits or tolerability observed for one gold formulation do not transfer automatically to another size, surface coating, dose, or route.

EVs provide a biological membrane interface and may carry intrinsic signaling activity in addition to an engineered payload. Their composition depends on source cells, isolation, processing, and storage. MISEV2023 recommends terminology that matches the evidence: a preparation should be called EVs rather than exosomes when endosomal biogenesis has not been established. Potency measurements should distinguish functional cargo association from free cargo or co-isolated material.

Table 1. Nanocarrier classes and the experimental questions they create

Platform	Design opportunity	Principal delivery question	Main interpretive limitation
Polymeric particles and polymersomes	Ligand density, degradation, controlled release	Does cargo leave the endothelium and reach its target compartment?	Particle degradation and payload release may occur in different locations.
Lipid nanoparticles and liposomes	Nucleic-acid protection and composition-dependent delivery	Is functional RNA delivery demonstrated in the intended cell?	Uptake or encapsulation alone does not establish cytosolic activity.
Gold and other inorganic particles	Elemental tracking or material-driven activity	Is the material a carrier, an active drug, or both?	Formulation-specific activity and persistence prevent class-wide conclusions.
Extracellular vesicles	Biological membrane interface and engineered cargo	Is the observed effect attributable to vesicles, cargo, or both?	Source heterogeneity and contaminants complicate causal attribution.
Hybrid formulations	Combined material and payload functions	Does the combination outperform dose-matched component controls?	Additional complexity can obscure the effective component.

Table 1 presents an interpretive comparison informed by the cited polymeric, lipid, inorganic, and EV studies; it does not assign a universal ranking.

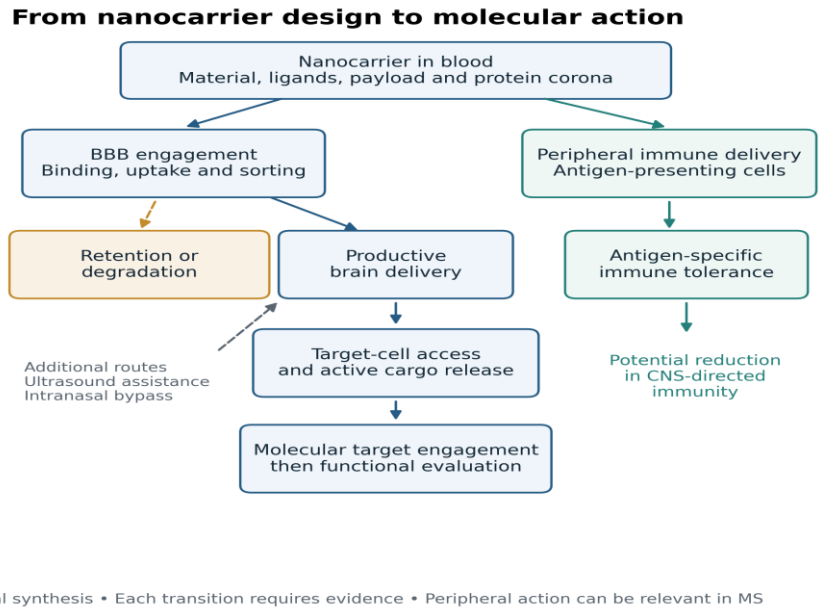

Figure 1. Conceptual relationships between nanocarrier design, BBB trafficking, target-cell access, and peripheral immune delivery. Arrows indicate pathways requiring experimental validation, not equivalent evidence levels. Peripheral immune action can be relevant in MS without substantial brain entry.

Mechanisms of BBB passage and intracellular delivery

Receptor-mediated transcytosis and binding geometry

Receptor-mediated transcytosis requires luminal recognition, internalization, intracellular sorting, and abluminal release. Each step can limit delivery. Earlier antibody experiments showed that lowering affinity for the transferrin receptor could increase brain uptake, while a monovalent molecular shuttle increased the penetration and activity of an attached therapeutic antibody. Such findings support receptor engineering, but antibodies and multiligand nanoparticles have different binding geometries and cannot be treated as interchangeable constructs.

Johnsen and colleagues reported parenchymal gold accumulation of 0.04, 0.08, and 0.23% injected dose per gram for anti-TfR-A, anti-TfR-D, and monovalent anti-TfR-A/BACE1 nanoparticles in mice. Their antibody dissociation constants were approximately 21, 149, and 22 nM, respectively. Thus, the monovalent construct's measured affinity resembled the high-affinity comparator; valency and affinity were distinct variables.

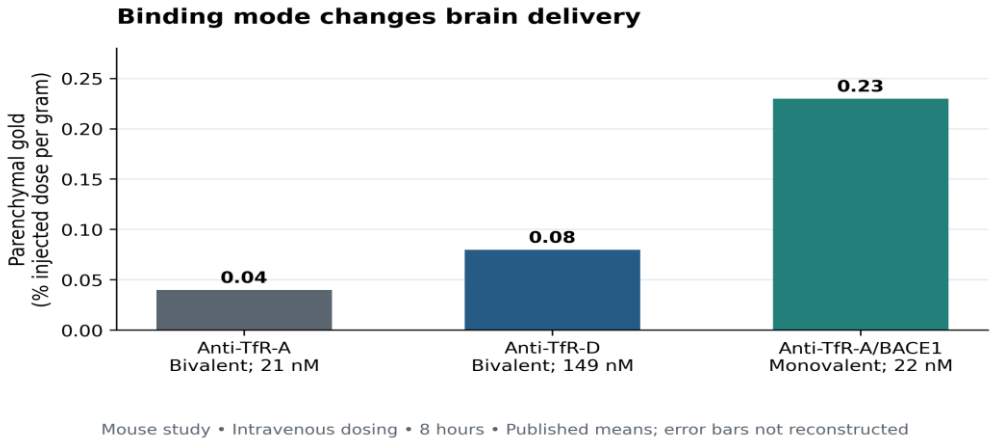

Figure 2. Parenchymal gold after intravenous dosing in mice at 8 h. Published means from Figure 5C of Johnsen et al.; n = 7–8. Numerical SEM values were not transcribed, so error bars are omitted. Labels report antibody dissociation constants, not whole-particle avidity.

Ligand density creates a further level of avidity beyond the affinity of an individual ligand. Tian and colleagues investigated LRP1-directed polymersomes and implicated syndapin-2, also called PACSIN2, in tubular transport that depended on cargo

avidity. This provides a mechanism through which surface organization can influence trafficking fate. It does not establish a universal ligand number for every particle or receptor. Changes in particle curvature, receptor abundance, or circulating proteins can change the effective interaction.

Caveolar transport and the limits of model transfer

Caveolin-dependent transport has been demonstrated for particular targeted systems. Tylawsky and colleagues used P-selectin-directed nanocarriers to induce caveolin-1-dependent passage into a medulloblastoma microenvironment. The tumor setting and the influence of radiation are essential to interpretation. This is mechanistic support for a transport route, not direct evidence that the same construct will cross an aged, non-tumor BBB in AD or PD.

A convincing receptor mechanism should therefore connect perturbation to transport. Competition, receptor knockdown, or pathway inhibition should reduce delivery without simply damaging the barrier. The interpretation becomes stronger when receptor abundance, intracellular localization, barrier integrity, and abluminal cargo are measured together. Merely observing colocalization with clathrin or caveolin identifies an association with a compartment; it does not demonstrate the complete transit route.

Adsorptive interactions and nutrient-transporter claims

Surface charge can alter particle association with cells, but greater association cannot distinguish receptor-independent adsorption from barrier injury. For a cationic formulation, productive transport should be assessed alongside endothelial viability and permeability to independent tracers. Charge measured in a simple buffer also may not represent the biological surface after exposure to blood. Corona experiments demonstrate that the biological interface can mask an engineered targeting ligand.

Nutrient-transporter targeting requires similar care. A surface glucose or amino-acid motif may increase binding or influence endocytosis, but a nanoparticle is not thereby shown to pass through the molecular substrate pathway of GLUT1 or LAT1. The proposed mechanism must explain how the whole construct, its released cargo, or both cross the cell. Here, transporter association is treated as a hypothesis requiring route-specific validation rather than as proof of intact-particle transport.

Extracellular vesicle uptake and transport

EV-mediated delivery can involve several interactions whose importance varies with the preparation and recipient cell. No single pathway should be assigned to all EVs from the presence of CD9, CD63, or CD81 alone. Vesicle identity, cargo association, cell uptake, and functional transfer require separate measurements. In particular, membrane-label fluorescence may persist or redistribute after vesicle disruption and should be supported by a payload-specific assay.

The RVG-targeted vesicle study by Alvarez-Erviti and colleagues provided an important functional example: systemic administration achieved BACE1 mRNA and protein knockdown in wild-type mouse brain. The experiment established a delivery and silencing proof of concept; it was not an AD clinical efficacy study. Later disease-specific EV work should be judged against the same requirement for demonstrated payload activity.

Physical assistance and routes that bypass the vascular BBB

Focused ultrasound with microbubbles can be combined with a nanoparticle formulation, but the resulting delivery is a property of the combination. Ultrasound parameters, bubble exposure, dosing time, and anatomical targeting become part of the intervention. The ALS study combining calcium-phosphate lipid nanoparticles with focused ultrasound illustrates this approach. A nanoparticle-only group and an ultrasound-only group are needed to identify their respective contributions.

Human focused-ultrasound investigations provide adjacent evidence. Lipsman and colleagues studied BBB opening in AD, and Rezai and colleagues subsequently combined regional opening with aducanumab in three participants. The latter study reported greater amyloid reduction in treated regions than homologous regions without ultrasound. These small investigations concern feasibility and regional pharmacodynamics; they neither validate a nanoparticle product nor establish a clinical benefit from nanocarrier delivery.

Intranasal administration presents a different causal question because it seeks access through nasal-associated pathways rather than necessarily crossing vascular endothelium. Sava and colleagues demonstrated regional HTT lowering after intranasal chitosan-siRNA administration in YAC128 mice. That finding supports functional nose-to-brain delivery in the tested model, but does not establish systemic BBB transcytosis. Human translation requires attention to nasal deposition, delivered volume, clearance, and regional coverage.

Protein corona and productive intracellular release

The protein corona can change the surface that cells encounter. Salvati and colleagues showed that a biomolecule corona could conceal transferrin targeting, while Schöttler and colleagues demonstrated that protein adsorption could contribute to a stealth phenotype. Together, these results undermine a simple assumption that all adsorbed protein is undesirable. They support measuring the composition and functional consequences of the actual biological interface. Neither study alone proves a particular corona-mediated BBB pathway.

Uptake is also distinct from endosomal escape. Imaging and trafficking studies of siRNA lipid nanoparticles identified inefficient cytosolic release and recycling as delivery constraints. Those foundational experiments were not demonstrations of brain-specific transport, but they explain why abundant particle-associated fluorescence can coexist with weak gene silencing. For RNA neurotherapeutics, functional delivery should be measured through sequence-dependent activity in the intended cell population.

Intracellular itinerary determines which delivery event is useful. Early endosomal sorting can be followed by progression toward degradative compartments or by recycling; Sahay and colleagues implicated recycling in the loss of internalized siRNA. Consequently, an endothelial uptake measurement should be followed by a destination measurement. Rab-associated compartment markers help describe trafficking, but a marker-positive particle is not thereby shown to have reached the brain-facing membrane or released an active payload.

The desired itinerary also changes with the therapeutic cargo. A lysosome-acidifying material needs access to the lysosomal lumen, whereas an siRNA must become available to cytoplasmic silencing machinery. A formulation optimized for escape could therefore be unsuitable for a material whose activity requires lysosomal retention. Conversely, successful delivery of a particle to lysosomes can represent treatment for a lysosomal defect or failure for an RNA payload. The carrier should be evaluated against its intended compartment rather than against uptake alone.

Table 2. Mechanistic claims and the evidence needed to support them

Claimed mechanism	Informative evidence	Common ambiguity	Interpretation supported
Receptor-mediated BBB transit	Receptor perturbation plus abluminal cargo and preserved barrier integrity	Strong endothelial binding	Receptor involvement in productive transport
Tubular or caveolar transport	Trafficking imaging plus pathway perturbation	Vesicle-marker colocalization alone	A route contributes in the tested model
Intact-particle brain entry	Capillary depletion plus orthogonal structural or elemental analysis	Whole-brain fluorescence	Extravascular material is present
Functional RNA delivery	Target-cell knockdown with sequence and carrier controls	High uptake or total tissue RNA	Active cargo reaches its molecular machinery
Intranasal brain delivery	Regional payload activity and deposition controls	Nasal or olfactory signal alone	Functional delivery through the tested route
Peripheral immune tolerance	Antigen-specific responses and mechanistic blockade	General cytokine suppression	Immune modulation can occur without BBB entry

The criteria in Table 2 are the present review's proposed interpretation framework, informed by the transport, RNA-delivery, and tolerization experiments discussed above. They are not a formal consensus grading scale.

Disease-specific molecular pathways

Alzheimer's disease

AD strategies can intervene at the vascular interface or within neural tissue. The former includes manipulating LRP1-associated transport to improve amyloid clearance. Chen and colleagues reported that angiopep-2-functionalized polymersomes with

tuned multivalency altered LRP1 trafficking and rapidly changed brain and plasma amyloid measurements in AD-model mice. Their work links receptor organization to a disease-relevant clearance mechanism rather than treating endothelial receptors solely as entry ports. The result remains a preclinical observation, and the receptor response to chronic exposure in patients is unresolved.

An intracellular strategy is to reduce amyloidogenic processing, as illustrated by BACE1-directed siRNA vesicles. However, changing the abundance of a disease-associated protein is not sufficient by itself to establish a useful therapy. The needed magnitude, duration, cellular distribution, and tolerability of suppression must be established. The historical vesicle experiment used wild-type mice and therefore informs functional delivery more directly than treatment of established AD pathology.

Inflammasome signaling provides another target. Heneka and colleagues implicated NLRP3 in AD-associated pathology and demonstrated protection in an APP/PS1 genetic model when the pathway was disrupted. NLRP3-associated activation of caspase-1 and maturation of interleukin-1β connect intracellular danger sensing to inflammatory output. A delivery strategy aimed at this process should therefore measure the activation step, not only total inflammatory protein abundance. A nanoparticle-induced fall in a downstream marker would not automatically demonstrate direct NLRP3 inhibition; pathway perturbation should establish necessity.

Tau-associated phosphorylation and proteostasis are reasonable candidate endpoints for future delivery studies, yet they should be tied to a defined payload and validated mechanism. Kinase activity, phospho-protein abundance, aggregation, and neuronal function measure different parts of the process. A decrease in a phospho-tau signal could follow reduced tissue injury without direct kinase inhibition. Similarly, improved lysosomal markers require evidence of productive degradation rather than simple accumulation of vesicular proteins. These are proposed evidentiary requirements, not claims of a demonstrated platform-wide effect.

The practical comparator is also changing. The lecanemab trial provides human evidence that amyloid-directed intervention can affect clinical decline in a selected population. It does not establish that faster amyloid removal through a nanoparticle is necessarily safer or clinically superior. Development should connect regional exposure to patient outcomes and monitor vascular consequences of altered clearance.

Parkinson's disease

PD delivery design must connect the intended region and cell type to an appropriate molecular intervention. Mazzulli and colleagues demonstrated a bidirectional relationship between glucocerebrosidase dysfunction and α-synuclein accumulation in experimental systems. Reduced glucocerebrosidase activity disturbed lysosomal lipid and protein handling, while accumulated α-synuclein further impaired the enzyme-related pathway. The implication is to restore or support glucocerebrosidase-dependent lysosomal function where deficient, rather than to inhibit glucocerebrosidase as a general therapeutic objective. This distinction is essential when describing the GBA1 pathway.

Bourdenx and colleagues investigated acidic nanoparticles that restored aspects of lysosomal acidification and function in disease-related systems. Their intracerebral animal administration bypassed the vascular delivery problem, so the experiments primarily establish intracellular therapeutic plausibility. A subsequent 2026 study by Lo and colleagues reported benefits from lysosome-acidifying nanoparticles in cellular and Drosophila α-synuclein models. These studies strengthen the argument for compartment-directed material activity while leaving systemic delivery to the human nigrostriatal system unresolved.

Wu and colleagues investigated functionalized lipid nanoparticles incorporating a borneol-based component and exenatide. The study reported brain distribution and changes in α-synuclein-associated pathology and AKT/GSK-3β-related measurements in PD-model mice. Because the formulation also altered BBB permeability, increased brain signal cannot be assigned entirely to receptor-mediated transport. Moreover, protein expression measurements do not by themselves identify the direction or necessity of a kinase-signaling mechanism.

Mitochondrial protection requires an additional level of localization. A particle can enter a neuron while failing to deliver an active agent to mitochondria. Studies proposing effects on PINK1/Parkin-mediated quality control should demonstrate mitochondrial turnover and relevant perturbation, rather than infer mitophagy from static protein abundance. These are development requirements for the proposed mechanism; the cited nanoparticle studies do not establish a general PINK1/Parkin effect. Functional endpoints should also distinguish short-term dopaminergic symptom relief from sustained protection of vulnerable neurons.

Huntington's disease

HD offers a comparatively direct nucleic-acid target because HTT expression can be measured after sequence-specific intervention. Delivery nevertheless remains regionally demanding. In the intranasal chitosan study, the amount of HTT

lowering varied with formulation and brain region. Figure 3 re-expresses two sets of published relative-expression data as percentage lowering, preserving the reported standard errors. The comparison demonstrates formulation-dependent distribution of pharmacodynamic activity rather than a universal efficiency for nose-to-brain treatment.

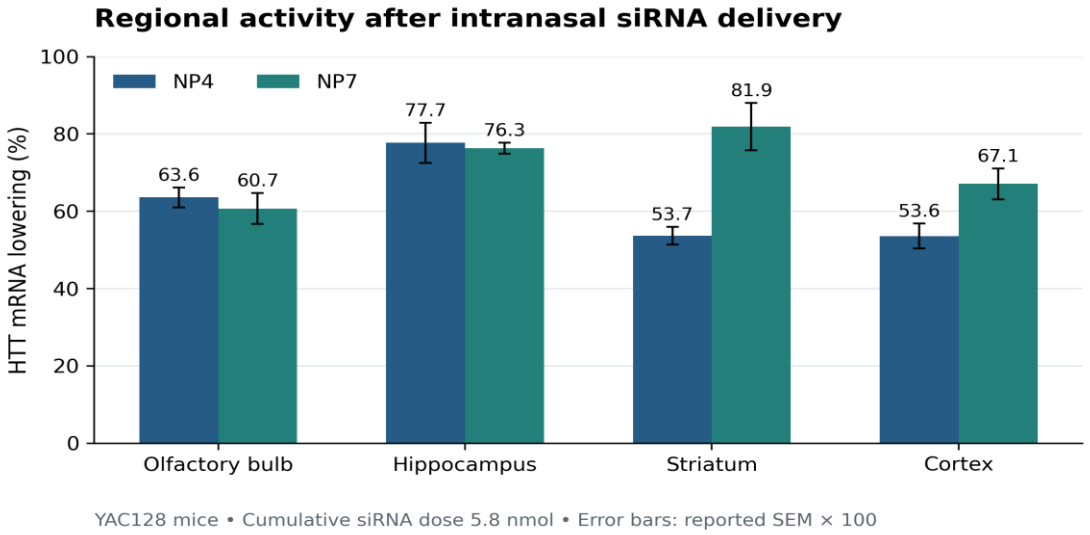

Figure 3. Regional HTT mRNA lowering for NP4 and NP7 in YAC128 mice, from Table 3 of Sava et al. Cumulative siRNA dose: 5.8 nmol; reported n = 4–6 per formulation. Lowering = −100 × published relative-expression change; error bars = 100 × reported SEM. These are complete formulations, not a single-variable comparison.

Follow-up kinetic work modeled the time course of HTT lowering after single and repeated intranasal nanoparticle dosing. This is relevant because the duration of a molecular effect determines the required dosing schedule. A high peak reduction measured soon after treatment may be less useful than stable exposure over an acceptable interval. Such modeling requires confirmation during chronic administration rather than extrapolation from a single short experiment.

Dual-function hybrid nanoparticles have also been investigated for HTT silencing and inflammatory modulation. Fihurka and colleagues combined an siRNA-containing chitosan matrix with a cannabidiol-containing lipid shell and examined cultured cells from a transgenic HD model. Their results support complementary activities in that cellular setting. They do not demonstrate intact BBB passage, organism-level efficacy, or an independently established combination benefit in patients.

A distinct 2026 study by Lee and colleagues investigated small PEG-coated gold nanoparticles as active material therapeutics in R6/2 mice. The reported mechanism involved p38α signaling, pyruvate dehydrogenase kinase 1 activity, oxidative phosphorylation, and pyroptosis-associated effects. Pyruvate dehydrogenase kinase 1 should be written out because its abbreviation PDK1 can otherwise be confused with a different kinase. The study broadens the HD nanotherapy rationale beyond gene silencing, while its model-specific activity and observed disposition require independent confirmation before clinical interpretation.

For HTT-lowering programs, future experiments should determine allele selectivity where applicable, quantify protein as well as mRNA, and examine whether striatal target engagement predicts durable functional benefit. A transcript reduction cannot establish selective removal of mutant protein unless the assay distinguishes relevant species. Material dose, cargo dose, and regional exposure should be reported together to support a meaningful therapeutic window.

Amyotrophic lateral sclerosis

ALS illustrates the importance of matching the payload to a molecular subtype. A SOD1-directed construct addresses SOD1 biology and should not be described as a treatment for every form of ALS. Tofersen binds SOD1 RNA and promotes its RNase-H-mediated degradation, reducing the template available for protein production. The tofersen trial demonstrated biomarker effects but did not meet its primary clinical endpoint at the specified 28-week analysis. This makes it an instructive example of the distinction between target engagement and a demonstrated functional outcome within a trial period.

The calcium-phosphate lipid nanoparticle study combined systemic delivery of a SOD1 antisense oligonucleotide with focused ultrasound and microbubbles in mice. It reported enhanced regional delivery, reduced SOD1 expression, and preservation-related neuronal findings. These results support studying a combined delivery system, while also identifying the need to assess

distribution beyond the sonicated brain region. Upper and lower motor-neuron coverage, spinal exposure, and repeated-treatment requirements cannot be inferred from brain signal alone.

Zheng and colleagues reported neural-stem-cell-derived EVs associated with antisense oligonucleotides in 2026. Their study assessed several administration routes, demonstrated molecular effects in ALS-related cellular models, and reported functional and neuronal benefits after intranasal treatment in SOD1-G93A mice. The work supports further investigation of EV-assisted delivery. Because source vesicles can themselves be bioactive, comparison with EV-only, free-ASO, and other carrier controls remains central to attributing benefit.

The same caution applies to TDP-43 and C9orf72. An intervention intended to modify a toxic species must distinguish that objective from removal of normal protein function. For these targets, disease-relevant cellular assays and transcript- or species-specific measurements are necessary before a general neuroprotective claim is credible. Similarly, proposed anti-ferroptotic activity should be tested with lipid-peroxidation measurements and mechanism-specific rescue; changes in bulk oxidative-stress markers alone are insufficient. These are priorities for future studies, not outcomes established across the included formulations.

Clinical nanomaterial evidence also prevents an entirely optimistic account. In the HEALEY ALS platform trial, the oral catalytic gold-nanocrystal suspension CNM-Au8 did not show benefit on the primary 24-week disease-progression endpoint. The disease rate ratio was 0.97, with a 95% credible interval of 0.783–1.175. Figure 4 displays this result with its uncertainty. CNM-Au8 was an active material rather than a payload-bearing delivery particle; its outcome does not decide the fate of all nanocarriers, but it demonstrates that mechanistic plausibility must be tested against clinical outcomes.

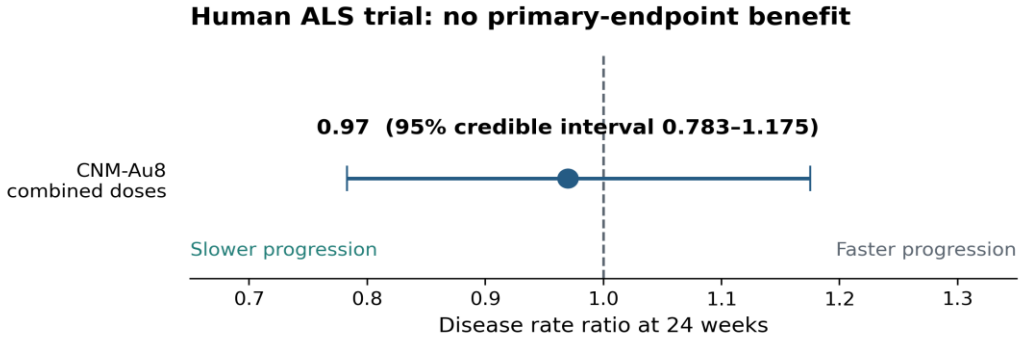

Figure 4. Primary 24-week disease rate ratio for combined CNM-Au8 doses versus pooled placebo in the HEALEY ALS trial. Point estimate 0.97; 95% Bayesian credible interval 0.783–1.175. The dashed line marks a ratio of 1. This active nanomaterial result is not an estimate for all nanocarriers.

Multiple sclerosis

MS is a particularly important exception to the assumption that brain entry is always the relevant delivery goal. A particle can act on peripheral antigen-presenting cells and alter subsequent CNS-directed immunity. Krienke and colleagues used noninflammatory, modified-mRNA lipoplexes encoding autoantigen in experimental autoimmune encephalomyelitis (EAE). Here, RNA delivery was intended to produce an antigen in an appropriate immunological context, rather than to silence a pathogenic transcript. Their work supports antigen-specific tolerization in mouse models, not a claim that a tolerogenic mRNA formulation must accumulate in brain parenchyma.

Nguyen and colleagues combined self-antigen delivery with ROS-scavenging cerium oxide nanoparticles in a tolerogenic biomaterial vaccine. They reported regulatory immune responses and improvement in EAE. The mechanistic question differs from neuronal RNA delivery: antigen presentation, immune-cell state, and specificity of the response are central. Reduced inflammatory infiltration can follow peripheral immune effects without establishing direct transport across the BBB.

Eixarch and colleagues investigated myelin-antigen-containing phosphatidylserine liposomes designed to mimic apoptotic material. Blocking regulatory cell populations and associated mediators disrupted the tolerogenic effect, strengthening mechanistic attribution within the EAE system. This approach illustrates the value of an intervention that tests necessity, rather than relying only on parallel changes in cytokines and disease scores.

Immune tolerance, antioxidant effects, and remyelination should nevertheless remain separate claims. Less inflammation can preserve existing myelin without generating new functional myelin. A proposed remyelinating formulation should examine oligodendrocyte-lineage responses, structural evidence, and functional recovery while accounting for axonal integrity. EAE

improvement supports preclinical development but cannot establish efficacy in heterogeneous relapsing or progressive human MS. Trials should also compare new interventions with relevant disease-modifying treatment rather than with an exclusively symptomatic baseline.

Table 3. Representative disease-specific primary evidence and its limits

Disease or context	System and model	Molecular or delivery finding	Limit of inference
BBB mechanism	TfR-targeted gold particles; mice	Binding mode changed parenchymal gold measurements	Material entry did not establish therapeutic benefit.
AD	LRP1-directed polymersomes; AD-model mice	Altered trafficking and amyloid clearance measurements	Human clearance and long-term benefit remain unestablished.
AD-relevant target	RVG-targeted vesicles; wild-type mice	Functional BACE1 silencing	Not a clinical AD efficacy experiment.
PD	Acidic polymeric particles; cellular and animal systems	Lysosomal pH and function were modified	Intracerebral dosing did not test systemic BBB transit.
PD	Functionalized lipid particles; PD-model mice	Brain distribution and synuclein-related changes	Permeability effects complicate transport attribution.
HD	Intranasal chitosan-siRNA; YAC128 mice	Regional HTT lowering	Route bypass and regional coverage require scale-up.
HD	PEG-coated gold particles; R6/2 mice	Bioenergetic and kinase-associated effects	Active-material findings are formulation-specific.
ALS	Lipid particles plus ultrasound; mice	SOD1-ASO delivery and pharmacodynamic effects	Combination treatment and anatomical coverage matter.
ALS	Stem-cell EV-associated ASO; cellular and mouse models	Target engagement and intranasal treatment effects	Carrier and cargo contributions need separation.
ALS	Oral gold nanocrystals; randomized human trial	No primary-endpoint benefit at 24 weeks	One material and regimen; not a class-wide verdict.
MS	Tolerogenic lipid or inorganic systems; EAE	Antigen-specific immune modulation	Peripheral effects do not prove BBB entry or remyelination.

What the quantitative examples demonstrate

The figures deliberately preserve their original experimental contexts. Figure 2 concerns material distribution after intravenous dosing; Figure 3 concerns regional RNA pharmacodynamics after intranasal dosing; Figure 4 concerns a clinical disease-progression estimate after oral treatment. Their axes, comparators, and biological meanings differ. Consequently, they must not be combined into a treatment-effect ranking or a pooled nanotherapy success rate.

In the TfR study, improved material entry did not produce detectable amyloid reduction under the assessment conditions. The graph contains published means without reconstructed error bars.

In the HTT example, percentage lowering is a transparent transformation of published relative-expression values, and the accompanying standard errors undergo the same multiplication by 100. Those errors describe the original small animal groups, not prediction intervals for human response. No new significance tests were performed. In the clinical example, the interval is Bayesian and remains explicitly labeled a credible interval; it is not presented as a frequentist confidence interval.

These examples support a development sequence: quantify exposure, establish molecular activity, and then test whether the activity improves a clinically relevant outcome. A negative result at a later stage should prompt investigation of exposure, dose, target relevance, and treatment timing. It should not be erased by emphasizing an earlier favorable biomarker.

Translational challenges

Human relevance of transport models

Model selection can change the apparent delivery mechanism. Lu and colleagues showed that some cells presented as pluripotent-stem-cell-derived brain microvascular endothelium instead exhibited epithelial identity, with vascular fate requiring additional specification. High electrical resistance therefore cannot serve as the sole validation of a human BBB model. Endothelial lineage, receptor expression, transport function, and response to perturbation should be examined together.

Cross-species testing should also measure the interaction actually used by the formulation. A ligand selected against a rodent receptor may behave differently against its human counterpart. Dose scaling by body mass does not correct an altered receptor affinity, abundance, or intracellular itinerary. Human-relevant binding and transport measurements should precede interpretation of large-animal efficacy. A model with a disrupted barrier may answer a disease-stage-specific question rather than predict delivery across an intact BBB.

Pharmacokinetics and anatomical coverage

The relevant pharmacokinetic quantities depend on the product. For a carrier, it is useful to distinguish circulating carrier, released drug, tissue-associated material, and pharmacologically available cargo. For an intrinsically active material, local material concentration and persistence may be more relevant. Total-brain concentration should be supplemented with regional and cellular measurements when target distribution is uneven.

For repeated treatment, peak exposure must be related to the interval of target suppression and the time required for recovery or toxicity. The HTT kinetic work illustrates why dosing schedules cannot be derived from a single favorable endpoint. A chronic program should report whether later doses reproduce delivery and whether tissue retention changes the response.

Safety and material fate

Safety evaluation should match the material, intended duration, and mechanism. The gold transport study showed substantial peripheral accumulation. [12] Acute normal histology does not determine the consequences of repeated exposure. A formulation intended for long-term treatment should connect clearance measurements to organ function, immune effects, and neurological assessment.

An intervention that modifies the BBB or induces membrane escape also needs a mechanism-linked safety evaluation. Beneficial payload activity and endothelial injury can both increase tissue-associated signal. With ultrasound combinations, regional exposure and vascular effects should be assessed together. With EVs, biological activity of the source preparation and the identity of accompanying material require characterization. These requirements follow from the proposed mode of action rather than a presumption that one carrier class is inherently safe.

Manufacturing and reproducibility

Material attributes that influence potency should be specified before scale-up. For a receptor-directed particle, ligand accessibility and effective avidity can matter as much as average ligand content. For an RNA formulation, protection, release, and functional delivery are separate attributes. For EVs, source, separation, composition, and biological potency require explicit control. MIRIBEL and MISEV2023 provide useful reporting foundations, while product-specific assays must establish which attributes predict activity.

Reproducibility also requires appropriate comparisons. Free cargo, empty carrier, non-targeted carrier, and combination components should be evaluated at relevant matched doses. When the carrier is intrinsically therapeutic, the empty-carrier comparison becomes a substantive intervention arm. A more elaborate construct should demonstrate why its additional components are necessary for the intended outcome.

Table 4. Proposed evidence package for translation

Development question	Recommended measurement	Decision enabled

Is the product reproducible?	Composition, size distribution, cargo integrity, ligand accessibility, potency	Define attributes that distinguish active batches.
Does the intended mechanism deliver cargo?	Receptor or pathway perturbation, barrier integrity, orthogonal distribution assays	Separate productive delivery from adhesion or injury.
Is the correct cell and compartment reached?	Regional and cell-resolved payload activity	Link administered dose to target exposure.
Does molecular activity improve disease-related function?	Dose response, target engagement, functional outcome, relevant comparator	Identify an exposure range worth advancing.
Can the regimen be repeated?	Serial pharmacokinetics, persistence, immune response, organ and neurological assessment	Establish a feasible chronic schedule.
Is a clinical test interpretable?	Defined population, pharmacodynamic marker, prespecified outcome and stopping criteria	Test a concrete therapeutic hypothesis.

Table 4 is a proposed development framework derived from this review. It is not a statement of jurisdiction-specific regulatory requirements.

Future research priorities

Future studies should select the delivery route from the therapeutic objective. A neuron-directed RNA therapy requires functional access to the appropriate neural population; a tolerogenic MS formulation may instead require reliable delivery to peripheral immune cells. Treating brain accumulation as the universal success criterion can favor the wrong product design. The experimental endpoint should correspond to the cell and compartment that mediate the intended benefit.

A second priority is causal evaluation of pathway claims. For a proposed NLRP3 mechanism, pathway-specific measurements and perturbations should accompany inflammatory outcomes. For lysosomal therapy, lumenal pH and degradative function should be distinguished. For a kinase-directed material, biochemical activity, cellular signaling, and functional consequences should form a coherent chain. Rescue experiments can identify whether the proposed molecular step is necessary rather than merely associated with benefit.

A third priority is clinically interpretable comparison. Nanocarriers should be tested against an appropriate route and formulation of the active cargo, including existing delivery approaches where relevant. Contemporary pharmacotherapies and human biomarker experience can guide comparator selection. Early clinical studies should establish product disposition and target engagement before interpreting exploratory functional changes as efficacy. A biomarker-selected population and a prespecified analysis are more informative than an undifferentiated claim that a carrier treats neurodegeneration.

Limitations of the review

This purposive narrative synthesis cannot estimate the prevalence of successful formulations, publication bias, or comparative clinical efficacy. Search and selection were not exhaustive, and the emphasis on accessible mechanistic primary studies may underrepresent negative, proprietary, or incompletely reported work. Most therapeutic examples were model-specific, and the presence of a human trial for one active nanomaterial does not validate other materials or payloads.

The plotted examples were selected for transparent numerical reporting and complementary endpoints, not because they represent the field statistically. Differences in route, dose, disease model, target, and follow-up prevent pooling. Some mechanistic arguments rely on foundational experiments outside the CNS or outside neurodegenerative disease; these are identified as supporting principles rather than direct efficacy evidence. The preserved abstract contains the separately identified inaccuracies and should be corrected before journal submission.

Conclusion

Nanoparticle-mediated neurotherapeutics can modify delivery, molecular activity, or both. The most useful evidence connects a defined formulation to a demonstrated route, an active payload or material, and a disease-relevant response. Receptor binding geometry and intracellular sorting help explain why strong endothelial association may fail to yield useful brain delivery. Corona formation, endosomal processing, administration route, and regional coverage further determine whether a molecular target is reached.

The disease-specific literature supports several testable directions: vascular amyloid clearance, lysosomal restoration in synuclein-associated systems, regional HTT silencing, subtype-directed ALS oligonucleotide delivery, and peripheral immune tolerization in MS. These directions have different delivery requirements and remain supported largely by preclinical evidence. The negative primary outcome of a human gold-nanocrystal ALS trial reinforces the need to evaluate clinical benefit directly. Translation will depend on reproducible products, causal mechanism testing, chronic exposure assessment, and clinical studies designed around a specific target and patient population.

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