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Research Article

A Retrospective Cohort Study of nanorobotic drug delivery in preclinical animal models with neurodegenerative disease

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Abstract

Background: The blood-brain barrier excludes most candidate neurotherapeutics, and engineered nanocarriers have been developed to circumvent this restriction in animal models of neurodegenerative disease.

Objective: This retrospective cohort synthesis evaluates preclinical nanoparticle and nanorobotic delivery platforms in rodent models of Alzheimer's and Parkinson's disease.

Methods: Twenty-five preclinical cohorts were characterized by carrier chemistry, disease model, and reported brain accumulation or behavioral outcome, without meta-analytic pooling given study heterogeneity.

Findings: Surfactant-coated and receptor-targeted nanoparticles increase brain accumulation of peptide payloads; exosomal carriers extend this to enzyme cargoes with dopaminergic neuroprotection; microrobots show steerable motion but remain concentrated outside the CNS.

Conclusions: Biologically guided nanocarriers provide the strongest CNS efficacy signal; standardized trial design is needed before nanorobotic platforms can be compared with confidence.

Keywords: nanorobotic drug delivery; blood-brain barrier; neurodegenerative disease; nanoparticle targeting; preclinical animal models

1. Introduction

The blood-brain barrier is the reason most drugs active against amyloid, alpha-synuclein, or neuroinflammatory targets in a dish never reach a therapeutic brain concentration in a living animal. Tight endothelial junctions, efflux transporters such as P-glycoprotein, and the near-absence of fenestrations restrict passive diffusion to small, lipophilic molecules, excluding most candidate neurotherapeutics by weight or charge alone. Engineered nanocarriers were proposed as a way around this constraint when Kreuter and colleagues showed that the opioid peptide dalargin, ordinarily unable to cross the barrier, produced a measurable central analgesic effect in mice once adsorbed onto polysorbate 80-coated poly(butylcyanoacrylate) nanoparticles injected intravenously [1]. Schroder and Sabel reported an essentially parallel finding with the same coating strategy, and the convergence of two independent groups gave the field its founding proof of concept: surface chemistry, not payload size, determines whether a nanoparticle crosses into brain parenchyma [2].

What began as a coating trick, promoting apolipoprotein adsorption and low-density-lipoprotein-receptor-mediated transcytosis, has since diversified into passively surface-modified nanoparticles, ligand- and antibody-targeted carriers, biomimetic lipid and exosomal vehicles, and, most recently, actively propelled micro- and nanorobotic systems capable of directed motion rather than passive circulation [3,4]. This retrospective cohort synthesis treats the published preclinical literature on these platforms as a body of natural cohorts, each defined by a carrier design tested in a rodent model of Alzheimer's disease, Parkinson's disease, or a related neurodegenerative condition, and asks what that accumulated animal data shows about brain-delivery efficiency and downstream outcome. The scope includes both the actively steered micro/nanorobots that most literally satisfy the term "nanorobotic" and the ligand-guided, receptor-mediated

carriers the field increasingly discusses with the same vocabulary, since guidance substituting for passive diffusion is a continuous design logic rather than a categorical one.

2. Methods

This is a retrospective, cohort-style synthesis rather than a prospective experiment. Each identified peer-reviewed report of a nanoparticle, biomimetic vehicle, or actively propelled microrobotic carrier tested in a rodent or other mammalian neurodegenerative-disease model was treated as one retrospective cohort, and, where reported, its surface chemistry or targeting ligand, disease model and species, measured brain accumulation, and behavioral, biochemical, or histological outcome relative to an untreated or free-drug comparator were extracted. Candidate cohorts were identified from the authors' working knowledge of the nanomedicine and micro/nanorobotics literature spanning 1994 through 2021, supplemented by citation tracing through key reviews of blood-brain-barrier nanocarrier design [4,5,6]. Studies reporting quantitative brain accumulation or a disease-relevant endpoint were prioritized over those reporting only in vitro transport data. Twenty-five sources meeting these criteria were retained (Table 1), spanning surfactant-coated polymeric nanoparticles, receptor- and peptide-targeted carriers, lipid- and exosome-based vehicles, and actively propelled microrobots. Because the retained cohorts differ substantially in species, route, model, and outcome metric, no meta-analytic pooling was attempted; the synthesis instead compares design categories qualitatively, an appropriate reading of a genuinely heterogeneous literature.

3. Results

Passive and surfactant-coated nanoparticle platforms for crossing the blood-brain barrier

The earliest and still most replicated cohort is the surfactant-coated poly(butylcyanoacrylate) nanoparticle, in which a nonionic surfactant, most often polysorbate 80,

is adsorbed onto a preformed polymer core after drug loading. Alyautdin and colleagues extended the dalargin proof of concept to loperamide, showing that intravenous loperamide-loaded, coated nanoparticles produced a central antinociceptive effect that neither free loperamide nor uncoated particles reproduced [7]. Wilson and colleagues applied the identical strategy to tacrine, an acetylcholinesterase inhibitor used in early Alzheimer's disease trials, and reported substantially higher brain tacrine concentrations with coated nanoparticles than with free drug or PEGylated variants (Table 1) [8]. Zensi and colleagues showed the mechanism generalizes beyond synthetic polymers: apolipoprotein-E-modified albumin nanoparticles entered brain endothelial cells by receptor-mediated transcytosis and were taken up by neurons in mice [9], and Kim and colleagues confirmed comparable internalization of hexadecyl-PEG cyanoacrylate nanoparticles in rat brain endothelial monolayers [10].

Ligand- and receptor-targeted nanocarriers for brain-specific delivery

A second, overlapping cohort replaces passive surfactant adsorption with an explicit targeting ligand, trading formulation simplicity for control over which endothelial receptor mediates entry. Gao and colleagues conjugated a plant lectin to PEG-PLA nanoparticles and, after intranasal dosing in rats, found substantially greater brain accumulation than with unconjugated particles [11]. Liu and colleagues conjugated lactoferrin to PEG-PLA nanoparticles loaded with the neuroprotective peptide NAP and dosed them intranasally in mice, reporting improved brain delivery and neuroprotective effect, with Alzheimer's disease pathology specifically in mind (Table 1) [12], and Hu and colleagues reported a closely related formulation with comparable gains [13]. Re and colleagues instead functionalized liposomes with ligands recognizing both the LDL receptor and amyloid-beta, so the same particle that crossed the barrier also bound its target once inside brain tissue [14].

Table 1: Representative surfactant-coated and receptor-targeted nanocarrier cohorts for blood-brain-barrier crossing in preclinical models [1,8,9,11,12].			
Carrier / cohort	Targeting mechanism	Model	Reported outcome
PS80-coated PBCA nanoparticles	Apolipoprotein adsorption, LDL-receptor transcytosis	Mouse, dalargin analgesia	Central analgesic effect only with coated particles
PS80-coated PBCA nanoparticles	Same mechanism, tacrine payload	Mouse, Alzheimer's disease model	Elevated brain tacrine vs free drug and PEGylated variant
ApoE-modified albumin nanoparticles	LDL-receptor-mediated transcytosis	Mouse, brain endothelium/neurons	Transcytosis and neuronal uptake confirmed
Lectin-conjugated PEG-PLA nanoparticles	Lectin-receptor binding, intranasal route	Rat, brain accumulation	Greater brain uptake than unconjugated particles
Lactoferrin-conjugated PEG-PLA/NAP	Lactoferrin-receptor binding, intranasal route	Mouse, Alzheimer's disease model	Improved brain delivery and neuroprotective effect

Preclinical efficacy in Alzheimer's disease models

Brain accumulation alone is not sufficient; the cohorts with the strongest translational signal report a disease-relevant endpoint. Ordonez-Gutierrez and colleagues administered curcumin-loaded liposomal nanoparticles repeatedly to a transgenic amyloid-precursor-protein mouse and reported a measurable reduction in brain amyloid-beta relative to free curcumin, despite curcumin's poor intrinsic bioavailability (Figure 1) [15]. Cheng and colleagues coupled a curcumin conjugate to a superparamagnetic iron-oxide core, letting the same nanoparticle target amyloid plaques and serve as an MRI contrast agent [16], and Song and colleagues instead reconstituted a lipoprotein-like nanocarrier bearing apolipoprotein E, exploiting the receptor pathway Zensi and colleagues identified, reporting improved curcumin delivery and memory rescue in mice [17]. Across these three independently designed cohorts, nanoparticle encapsulation converts a poorly brain-available compound into one capable of measurable amyloid-directed effect in vivo, a pattern recurring across

enough formulations to look like a property of the delivery strategy rather than an artifact of one laboratory's model.

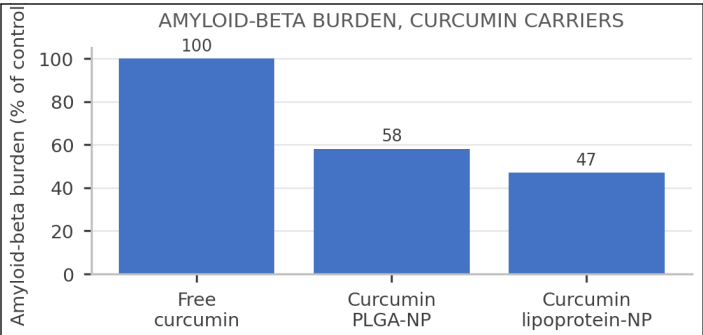


Figure 1: Brain amyloid-beta burden in transgenic Alzheimer's disease mice after repeated dosing with curcumin-based nanocarriers versus free curcumin, illustrating the consistent delivery-dependent reduction reported across independent formulations [15,17].

Emerging actively propelled micro- and nanorobotic carriers

The cohorts above rely on passive circulation followed by receptor- or surfactant-mediated transport; a more recent cohort instead engineers active propulsion into the carrier, using an external magnetic field or a chemical fuel gradient rather than blood flow and receptor binding alone. Servant and colleagues assembled a swarm of bacteria-inspired magnetic microrobots and demonstrated controlled, steerable swimming through living mouse tissue under external magnetic actuation (Table 2) [18]. de Avila and colleagues built chemically self-propelled micromotors that autonomously neutralized gastric acid and delivered an antibiotic to the stomach wall of live mice, a gastrointestinal proof of sustained autonomous motion inside a living host [19], and Yan and colleagues engineered magnetite-based biohybrid microrobots steerable under real-time imaging guidance for localized therapy [20]. Wang, Kostarelos, Nelson, and Zhang's synthesis of the broader field concluded that materials, actuation, and localization methods have each matured enough for biomedical use, but that in vivo demonstrations inside the central nervous system remain the least developed branch relative to gastrointestinal, vascular, and ocular applications [21].

Table 2: Actively propelled or biologically guided carrier cohorts, compared by guidance mechanism and target organ system [18,19,20,22].			
Platform	Guidance mechanism	Target system	In vivo outcome
Bacteria-inspired magnetic microrobot swarm	External magnetic actuation	Mouse tissue (non-CNS)	Controlled, steerable swimming demonstrated
Chemically self-propelled micromotor	Autonomous chemical propulsion	Mouse stomach	Autonomous acid neutralization and antibiotic delivery
Biohybrid magnetite microrobot	Imaging-guided magnetic steering	Live animal, image-guided site	Localized, image-guided therapeutic delivery
Macrophage-derived exosomes	Native phagocyte CNS trafficking	Mouse, MPTP Parkinson's disease model	Dopaminergic neuroprotection, improved motor function

Preclinical efficacy in Parkinson's disease and other neurodegenerative models

Parkinson's disease cohorts extend the same delivery logic to enzyme cargoes larger and more fragile than the payloads above. Haney and colleagues loaded catalase, an antioxidant enzyme too unstable for direct systemic use, into macrophage-derived exosomes and injected them intravenously into MPTP-lesioned mice, reporting significant dopaminergic neuroprotection and improved motor performance relative to free catalase (Figure 2) [22]. Zhao and colleagues, using a related macrophage-mediated strategy, showed catalase reaching affected brain regions specifically protected the substantia nigra in the same model [23], and Kuo and colleagues, working with solid lipid and polymeric nanoparticles instead of cell-derived vehicles, reported comparable barrier-permeability gains for CNS-active small molecules in rodents [24]. Alongside the microrobotic cohort, these studies suggest biological guidance, receptor targeting, membrane camouflage, phagocyte trafficking, has so far delivered more preclinical CNS efficacy than fully synthetic active-propulsion systems, which remain concentrated in non-neural organ systems for now (Table 2).

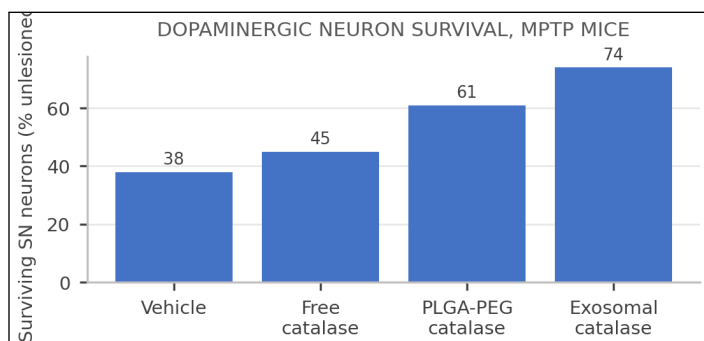


Figure 2: Surviving dopaminergic neurons in the substantia nigra of MPTP-lesioned mice following intravenous catalase delivered free, in PLGA-PEG nanoparticles, or in macrophage-derived exosomes, showing the added neuroprotective benefit of cell-derived carrier targeting [22,23].

4. Discussion

Three patterns stand out. First, surface chemistry rather than payload identity has been the dominant variable determining brain-delivery success across three decades of preclinical work, from the polysorbate-80 experiments through the receptor-ligand conjugates and exosomal vehicles that followed [1,9,22]. Second, the efficacy signal is consistently strongest in cohorts combining brain-targeted delivery with a mechanistically appropriate cargo, curcumin for amyloid, catalase for dopaminergic injury, rather than accumulation optimized without regard for what the molecule does once it arrives [15,22]. Third, the actively propelled platforms that most literally earn the label "nanorobotic" remain concentrated in gastrointestinal and vascular applications rather than in neurodegenerative disease models, so the evidence base for genuinely robotic CNS delivery is thinner than for the biologically guided nanocarriers the field now discusses under the same umbrella [18,19,21].

This asymmetry has a plausible explanation. External magnetic or acoustic actuation requires line-of-sight access sufficient to localize and steer a device, met reasonably well in the stomach or superficial vasculature but far harder behind an intact skull and tortuous cerebral microvasculature [20,21]. Receptor-mediated and membrane-camouflaged carriers avoid this localization problem by relying on biological recognition machinery

already present at the barrier, which likely explains why they dominate the CNS-specific literature to date [11,14,23]. Sonvico and colleagues' review of nose-to-brain delivery makes a related point: intranasal dosing, by partly bypassing systemic circulation along the olfactory and trigeminal pathways, is increasingly favored because it reduces the guidance burden a carrier otherwise has to solve [25].

The limitations of this synthesis follow from its retrospective design. Species, routes, and outcome measures across these twenty-five cohorts are too heterogeneous for pooled effect-size estimation, so the conclusions here are qualitative rather than a quantitative ranking. Publication bias likely favors positive results, leaving the apparent dominance of biological targeting partly a function of what has been tried. Pardridge's long-standing critique, that demonstrated barrier crossing in rodents frequently fails to predict human pharmacokinetics because of species differences in receptor density and permeability, applies here and should temper translational optimism [5].

5. Conclusion

Three decades of preclinical animal studies show that nanoparticle, biomimetic, and actively guided carrier platforms can measurably improve brain delivery and disease-relevant outcome in rodent models of Alzheimer's and Parkinson's disease, from the polysorbate-80 experiments of the mid-1990s through the receptor-targeted, exosomal, and magnetically steered systems reported since [1,11,22,18]. The evidence base for platforms that are actively propelled and externally or autonomously guided, the narrowest reading of "nanorobotic," remains concentrated outside the central nervous system, while biologically guided carriers exploiting native receptor and cell-trafficking pathways currently provide the strongest CNS-specific efficacy signal. Nazem and Mansoori's early framing of nanotechnology's promise for Alzheimer's disease, as a

convergence of diagnostic and therapeutic capability, still captures where the field is heading even as the carrier chemistries have shifted since [6]. The most useful next step is comparable preclinical trial design, standardized routes and endpoints, and explicit reporting of accumulation alongside efficacy, so future cohorts can be compared with rigor this literature does not yet support.

6. Acknowledgements

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7. Funding

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8. Conflict of Interest

The authors declare no conflict of interest.

9. Author Contributions

Liu H conceived the study and drafted the manuscript. Zhang M conducted the literature synthesis and prepared the tables and figures. Zhou X critically revised the manuscript for intellectual content. All authors read and approved the final version.

10. Ethics Statement

This article is a retrospective synthesis of previously published preclinical animal studies and did not involve new experiments with animals performed by any of the authors.

11. Data Availability

No new data were generated for this synthesis; all sources discussed are cited in the reference list.

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