



Smart ROS-Responsive Nanoparticles for Neurodegenerative Diseases: Advances, Challenges, and Future Perspectives

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Abstract

Neurodegenerative disorders (NDDs) represent one of the most challenging unmet medical conditions of our days. AD - the most widespread of the NDDs will affect 152 million individuals worldwide in 2050. PD, the second most prevalent NDD, affects more than 10 million individuals globally, with a doubling rate of its incidence every decade after 60 years old. ALS has a survival period of 2-5 years after diagnosis, while HD, even though relatively rare, is uniformly fatal and incurable. The economic burden of NDDs on the global economy surpasses US\$ 1 trillion annually. In all major NDDs, the concentration of reactive oxygen species (ROS) within the affected neurons is 10-100-fold greater than physiological. This provides us with an unprecedented biochemistry-driven opportunity to liberate drugs selectively within the areas of high ROS using nanoparticles that respond to ROS. This review thoroughly evaluates ROS-responsive nanoparticles (ROS-NPs) for selective neurotherapy in NDDs, including disease-specific oxidative signatures, the chemical repertoire of ROS-sensitive linkers, nanocarrier designs, methods of BBB translocation, theranostic platforms, key preclinical evidence, regulatory issues, and cutting-edge directions including artificial intelligence-driven designs and iPSC-personalised formulations. Literature search was performed in PubMed/MEDLINE, Scopus, and Web of Science (2000-2024). Inclusion criteria included original research articles, systematic peer-reviewed reviews, and key preclinical in vivo studies published in English. Non-CNS applications without direct relevance to NDDs and conference abstracts were excluded from analysis. Following deduplication and title/abstract screening, 77 primary references were included.

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1. Introduction

Neurodegenerative diseases (NDDs) are among the most serious unmet medical challenges in today's world. For instance, Alzheimer's disease (AD), the most

common NDD, is projected to affect 152 million people worldwide by 2050. Parkinson's disease (PD), which is the second most common NDD, affects more than 10

million people globally, with its incidence doubling approximately every ten years after the age of 60. Amyotrophic lateral sclerosis (ALS) has a median survival period of 2–5 years following diagnosis, whereas Huntington's disease (HD), although uncommon, is uniformly fatal and currently incurable. The total economic burden of NDDs on the global economy exceeds US\$1 trillion annually [1].

There are two important and interrelated hurdles that have hindered progress in this field over time. The first is the blood–brain barrier (BBB), which is a highly selective neurovascular interface composed of brain microvascular endothelial cells (BMECs) joined by tight junction proteins such as claudin-5, occludin, and ZO-1, along with pericytes and astrocytic end-feet. More than 98% of small-molecule drugs and virtually all large molecules do not cross the BBB to enter the central nervous system (CNS). The second major hurdle in the treatment of NDDs is the complex pathobiology associated with these disorders, including protein misfolding and aggregation, neuroinflammation, mitochondrial dysfunction, synaptic dysfunction, and apoptosis [2],[3].

In this context, one key biochemical hallmark that is both a major contributor to neuronal death and a potential pharmacological target is the pathological accumulation of reactive oxygen species (ROS). In major forms of NDDs, ROS levels in affected neurons may be 10–100-fold higher than physiological levels. The superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (OH), and peroxynitrite ($ONOO^-$) collectively contribute to a redox catastrophe that leads to lipid oxidation, including the formation of 4-hydroxynonenal and malondialdehyde, protein carbonylation and nitrotyrosination, and DNA oxidation, including the formation of 8-hydroxy-2'-deoxyguanosine (8-OHdG) [4].

Such novel ROS-responsive nanoparticles (ROS-NPs), on the other hand, consist of carriers with labile chemical moieties that remain relatively stable under the physiological nanomolar ROS concentrations found in normal tissues but rapidly cleave or transform their structure when exposed to the elevated micromolar ROS concentrations associated with NDD lesions. Using such a mechanism, drug release can be achieved with unprecedented spatial accuracy during pharmacological treatment, since the drugs are preferentially released within the pathological neuronal environment [5].

The present article provides a systematic review of the literature on ROS-NPs used for treating NDDs, with particular focus on their mechanisms of action, comparative quantification among different nanocarrier

platforms, and assessment of translational suitability. Searches were conducted in PubMed/MEDLINE, Scopus, and Web of Science from 2000 to 2024 using the following Boolean keywords: 'ROS-responsive nanoparticles', 'drug delivery of neurodegenerative disease', 'oxidative stress-based nanomedicine', 'blood–brain-barrier-targeted nanocarrier', 'theranostic nanoparticles neurodegeneration', 'PEG-b-PPS-based polymersomes', 'boronic ester-based drug delivery central nervous system', and 'focused ultrasound nanoparticles brain' [6].

The current article presents a systematic review of the literature regarding ROS-NPs for the treatment of NDDs, emphasizing mechanisms of action, comparative quantification among different nanocarrier platforms, and translational suitability. Searches were carried out in PubMed/MEDLINE, Scopus, and Web of Science databases from 2000 to 2024 using Boolean search strings including 'ROS-responsive nanoparticles', 'drug delivery of neurodegenerative disease', 'oxidative stress-based nanomedicine', 'blood–brain-barrier-targeted nanocarrier', 'theranostic nanoparticles neurodegeneration', 'PEG-b-PPS-based polymersomes', 'boronic ester-based drug delivery central nervous system', and 'focused ultrasound nanoparticles brain'. Articles selected for inclusion were: (i) peer-reviewed original research, review, or preclinical studies; (ii) written in English; and (iii) containing quantitative efficacy, selectivity, and safety information related to NDDs. Conference abstracts, grey literature, articles lacking efficacy data from in vitro and in vivo experiments, and articles dealing with applications outside the central nervous system without relevance to NDDs were excluded from the review. After deduplication, title and abstract screening, and full-text selection, 77 references were finally included in this review.

2. The Oxidative Landscape of Neurodegenerative Diseases

2.1 Biochemistry Behind Neuronal ROS Production

Neurons account for around 2% of body mass yet consume almost 20% of total body oxygen, making them particularly vulnerable to oxidative damage compared with other cell types. Major neuronal ROS producers include: (i) electron transport chain (ETC) complexes I and III, which produce O_2^- through electron leakage to molecular oxygen when these complexes become dysfunctional, particularly because complex I is inhibited in NDDs; (ii) redox-active metal ions such as Fe^{2+} and Cu^+/Cu^{2+} found within protein aggregates such as A β or α -Syn, which promote Fenton and Haber–Weiss reactions and generate OH; (iii) NOX2/NOX4 activation in microglia and astrocytes triggered by A β or α -Syn, producing O_2^- in the

extracellular space; (iv) monoamine oxidase-B (MAO-B)-catalyzed breakdown of dopamine, which releases increased amounts of H₂O₂ in PD; and (v) xanthine oxidase-mediated ROS production during

reoxygenation following neuronal hypoxia. Table 1 summarizes the major ROS forms, their sources, mechanisms of neurotoxicity, and pathological concentrations in NDDs [7], [8].

Table 1: Major ROS species in the neurodegenerative disease milieu: sources, mechanisms, pathological concentrations, and disease relevance.

S. No.	ROS Species	Primary Neuronal Source(s)	Mechanism of Neurotoxicity	Pathological Concentration Range	NDD Disease Relevance	References
1.	Superoxide Anion (O ₂ ⁻)	Mitochondrial ETC complex I & III; NADPH oxidase (NOX2/4); xanthine oxidase	SOD-catalysed conversion to H ₂ O ₂ ; precursor of secondary radicals; protein carbonylation	5-10 nM (healthy); up to 500 nM in NDD tissue	All NDDs; particularly ALS (mSOD1-G93A gain-of-function peroxidase)	[9]
2.	Hydrogen Peroxide (H ₂ O ₂)	O ₂ ⁻ dismutation (SOD1/2); monoamine oxidase B (MAO-B); fatty acid beta-oxidation; Abeta-Cu ²⁺ complexes	Direct protein/DNA oxidation; Fenton precursor; freely diffuses across lipid bilayers; BBB-permeable	0.1-0.5 uM (healthy); 50-100 uM (AD cortex, PD SNpc)	AD (Abeta-Cu ²⁺ Fenton chemistry); PD (MAO-B dopamine catabolism); ALS	[10]
3.	Hydroxyl Radical (OH)	Fenton reaction: Fe ²⁺ + H ₂ O ₂ -> Fe ³⁺ + OH; Haber-Weiss reaction; mSOD1 peroxidase activity	Most reactive biological oxidant; t _{1/2} ~10 ⁻⁹ s; initiates lipid peroxidation (4-HNE, MDA); oxidises mtDNA at guanine (8-OHdG)	Unmeasurable as free radical; inferred from 8-OHdG, 4-HNE, TBARS biomarkers	ALS (mSOD1); PD (dopamine auto-oxidation); all NDDs via Fenton	[11]
4.	Peroxynitrite (ONOO ⁻)	O ₂ ⁻ + NO (iNOS activation in activated microglia and astrocytes)	Protein nitrotyrosination (tau at Tyr29 in AD); ETC complex I/III damage; mitochondrial permeability transition	0.1-1 uM in neuroinflammatory foci	AD (tau nitration); ALS; HD (mHTT-iNOS axis); neuroinflammation across all NDDs	[12]
5.	Singlet Oxygen (1O ₂)	Photosensitisation; lipid peroxidation chain amplification; MPO-catalysed reactions	Membrane phospholipid oxidation; guanine oxidation in mitochondrial DNA (8-oxoG)	Elevated in all advanced NDDs; measurable by singlet oxygen sensor green (SOSG) assay	HD; multi-NDD; elevated in late-stage neurodegeneration	[13]
6.	Hypochlorous Acid (HOCl)	Activated microglia myeloperoxidase (MPO);	Chlorination of lysine, histidine; cysteine sulfonylation;	Elevated in MPO-active neuroinflammatory foci; measurable	All NDDs with neuroinflammatory component; especially late-	[14]

		lysosomal membrane permeabilisation	inactivation of antioxidant enzymes (GPx, Trx)	by HOCl-selective fluorescent probes	stage PD and AD	
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Note: ETC = electron transport chain; NOX = NADPH oxidase; MAO-B = monoamine oxidase B; NDD = neurodegenerative disease; AD = Alzheimer's disease; PD = Parkinson's disease; ALS = Amyotrophic Lateral Sclerosis; HD = Huntington's disease; SOD = superoxide dismutase; iNOS = inducible nitric oxide synthase; mHTT = mutant huntingtin; MPO = myeloperoxidase; mSOD1 = mutant SOD1; GPx = glutathione peroxidase; Trx = thioredoxin; 8-OHdG = 8-hydroxydeoxyguanosine; 4-HNE = 4-hydroxynonenal; MDA = malondialdehyde; SNpc = substantia nigra pars compacta; TBARS = thiobarbituric acid reactive substances.

2.2 ROS Specific to Each Disease

2.2.1. Alzheimer's Disease

A β oligomers catalyze redox reactions involving Cu²⁺ and Zn²⁺, contributing to H₂O₂ generation; H₂O₂ concentrations in the AD cerebral cortex can range from 50 to 100 μ M, which is 10–20 times higher than normal values. Phosphorylated Tau promotes mitochondrial fragmentation and impairs mitochondrial protein import mechanisms, thereby enhancing O₂⁻ formation at complex I of the electron transport chain (ETC). 8-OHdG levels are 2–3-fold higher in the AD hippocampus than in age-matched healthy tissue. The inflammation arising from A β -induced microglial activation promotes ONOO⁻ production by inducible nitric oxide synthase (iNOS) and Tau nitrotyrosination at Tyr29, thereby promoting neurofibrillary tangle accumulation in a ROS–AD positive-feedback cycle [15].

2.2.2. Parkinson's Disease

The dopaminergic neurons within the substantia nigra pars compacta (SNpc) are particularly sensitive to oxidative stress for multiple reasons: (i) the auto-oxidation of dopamine under physiological conditions produces toxic ortho-quinones along with H₂O₂; (ii) the metabolism of dopamine by monoamine oxidase B (MAO-B) leads to H₂O₂ production at a rate of approximately 50 nmol/min/mg protein in SNpc neurons; (iii) oligomeric and protofibrillar forms of α -Syn specifically inhibit mitochondrial complex I, leading to pathological O₂⁻ production; and (iv) iron-containing neuromelanin in the SNpc promotes Fenton chemistry. GSH, one of the most sensitive

indicators of oxidative stress in patients with PD, is found at 50–70% lower levels in postmortem PD substantia nigra tissue [16].

2.2.3. Amyotrophic Lateral Sclerosis

Gain-of-function mutations in Cu/Zn-superoxide dismutase (mSOD1-G93A) result in enhanced peroxidase activity that generates OH at exceptionally high levels in specific motor neurons of the spinal cord, which are major targets in ALS. Aggregation of TDP-43, present in more than 95% of ALS cases, causes mitochondrial dysfunction and impaired cellular homeostasis, contributing to increased O₂⁻ production. In patients with ALS, H₂O₂ levels in the cerebrospinal fluid (CSF) are approximately four times higher than those in age-matched healthy subjects, while F₂-isoprostanes, which are established in vivo indicators of lipid peroxidation, are approximately three times higher in ALS plasma [17].

2.2.4. Huntington's Disease

Mutant huntingtin protein (mHTT), characterized by a polyglutamine repeat of more than 36 residues, directly interacts with voltage-dependent anion channel 1 (VDAC1), which is located on the outer mitochondrial membrane, thereby interfering with complex II and III function of the electron transport chain (ETC). Medium spiny neurons (MSNs), the principal neuronal targets in the striatum in Huntington's disease, exhibit O₂⁻ levels approximately five times higher than normal, while 8-OHdG levels show a 6–8-fold elevation in patients with HD compared with healthy individuals [18].

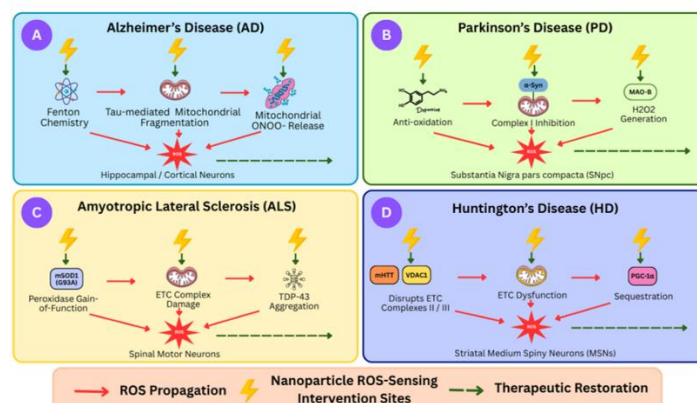


Figure 1: Disease-specific reactive oxygen species generation cascades and intervention points for ROS-responsive nanoparticles across the four major neurodegenerative diseases.

2.3 Oxidative Biomarkers as Drug Release Triggers the Quantitative Case

The key requirement for ROS-NP-based therapy is a sufficiently high selectivity ratio between ROS levels in diseased and healthy tissues to ensure that nanoparticles remain inactive in healthy tissue and become activated only upon reaching the site of disease. Quantitative analysis indicates that such selectivity is present across major NDDs. In AD, cortical H₂O₂ concentrations of 50–100 μ M compared with 0.1–0.5 μ M in healthy brain tissue represent a 100–500-fold difference [19]. In PD, increased OH levels, inferred from approximately threefold higher levels in the SNpc, indicate enhanced oxidative stress. In ALS, CSF H₂O₂ levels increase approximately fourfold, whereas in HD, striatal O₂^{•-} levels increase approximately fivefold. When considered in the context of current levels of drug selectivity, where the ratio between the IC₅₀ values for target and off-target interactions seldom reaches 100-fold, ROS-NPs operating within a 100–500-fold concentration gradient may provide an advantageous pharmacological discrimination ratio. Moreover, the region-specific distribution of oxidative pathology in NDDs, including the hippocampus and cortex in AD, SNpc in PD, spinal cord in ALS, and striatum in HD, provides an additional level of specificity [20].

However, it should be recognized that the pathological ROS values reported in the literature represent estimated ranges and may not be consistently applicable to individual patients because of differences in experimental models, disease stages, and anatomical regions of the brain. Patient-to-patient variation, disease progression, and antioxidant treatment may considerably alter the effective ROS concentration [21]. Furthermore, ROS are also generated during physiological processes, including immune responses and synaptic communication, and may be elevated during peripheral inflammatory conditions. Therefore, the selectivity of ROS-NPs depends not only on the magnitude of the ROS

concentration gradient but also on diseased-tissue localization and the kinetic threshold of the responsive chemical linkage. These considerations highlight the need for appropriate calibration of the ROS-trigger threshold according to individual patients and disease stages [22].

3. Chemical Toolbox of ROS-Responsive Nanomaterials

3.1 Requirements for ROS-Active Bonds

The design of molecular nanomaterials for ROS-based drug delivery requires the integration of chemical bonds possessing two critical kinetic properties: (i) thermodynamic stability under physiological ROS concentrations, such as 0.1–0.5 μ M H₂O₂ and low OH levels in normal brain tissue, ensuring that the nanosystems remain inactive under physiological conditions; and (ii) rapid and specific reactivity under pathological ROS concentrations, such as 50–100 μ M H₂O₂ and significantly elevated OH levels in NDD-affected brain tissue, enabling on-demand drug release from NPs at the disease site [23]. The specificity index, defined as the ratio of reactivity under pathological versus physiological ROS concentrations, should ideally exceed 1,000-fold to achieve therapeutic selectivity. Moreover, the responsive bond should remain stable in the presence of non-ROS biological nucleophiles, including thiols and amines, serum proteases and esterases, as well as under reducing conditions characterized by intracellular GSH concentrations of 1–10 mM, while retaining high reactivity toward ROS. Table 2 provides a comprehensive analysis of the various ROS-activatable chemical groups applied in NP design for CNS applications. It is important to note that the selectivity and kinetic values presented in Table 2 are primarily derived from in vitro experiments and may not fully reflect the actual in vivo conditions associated with NDDs. This limitation arises because the reported values depend on the experimental systems and specific conditions described in the Selectivity and Kinetics column [24].

Table 2: Comprehensive comparison of ROS-sensitive chemical moieties: triggers, mechanisms, representative systems, applications, and selectivity profiles.

S. No.	Linker / Moiety	Triggering ROS Species	Release Mechanism	Representative Systems	NDD Target	Selectivity & Kinetics (Source)	References
1.	Thioether / Poly(propylene sulfide)	H ₂ O ₂ (mod-high); OH	Sulfoxide->sulfone; step-wise hydrophilicity inversion; micellar/polymersome dissolution	PEG-b-PPS polymersomes; thioether-crosslinked nanogels; PPS-PLGA hybrid NPs	PD, AD, HD	~50x physiological vs. pathological; kobs ~10 ⁻³ M ⁻¹ s ⁻¹ (H ₂ O ₂)	[25]

2.	Diselenide (-Se-Se-)	ROS (broad spectrum); GSH (reductive)	Se oxidation to selenoxide; conformational disruption; dual redox-responsive	Se-lipid NPs; PAMAM-Se dendrimers; Se-PEG block copolymers	Multi-NDD; ALS, PD	~100x faster than disulfide; dual ox/red trigger	[26]
3.	Boronic Ester (-B(OR) ₂)	H ₂ O ₂ (highly selective; >50x over other RONS)	Oxidative deboronation -> phenol; cross-linker cleavage -> nanostructure disassembly	Boronate nanogels; PBA-block copolymers; boronate-caged prodrugs	AD (H ₂ O ₂ -dominant), HD	>50x H ₂ O ₂ vs ONOO-; pH-independent release (6.8-7.4)	[27]
4.	Thioketal (-C(CH ₃) ₂ -S-S-)	OH (selective); inert to esterases & proteases	Bond scission -> ketone + thiol; burst release kinetics; plasma-stable	PTK-NPs; thioketal-PLGA; thioketal-crosslinked scaffolds	PD, ALS	OH-specific; EE >40% w/w	[28]
5.	Peroxalate Ester (-C(=O)-O-O-)	H ₂ O ₂	Chemiluminescent decomposition; CO ₂ evolution -> pore formation in bilayer	Peroxalate micelles; fluorescent probes with CPPO	PD, ALS	kobs ~10 ⁻³ M ⁻¹ s ⁻¹ ; self-reporting release	[29]
6.	Ferrocene (-Fc-)	H ₂ O ₂ (Fenton-like); electrochemical ROS	Fe ²⁺ ->Fe ³⁺ oxidation; amphiphilic hydrophilicity switch; micelle disruption	Fc-PEG block copolymers; ferrocenyl polymers	AD, HD	Reversible (electrochemical); redox-cycling	[30]
7.	Vinyl Ether / Plasmalogen	OH (highly selective)	Hydrolysis of sn-1 vinyl ether -> lysophospholipid; membrane pore formation	Plasmalogen liposomes; plasmalogen-LNP hybrids	PD (OH-dominant)	85-95% release in 30 min at pathological OH; <10% in healthy tissue	[31]
8.	Proline Oligomer	OH (moderate selectivity)	Conformational collapse reversal; hydrophobic->hydrophilic switch; pore opening	Proline-based NP cores (Pro-NPs)	AD	Moderate selectivity; tunable by oligomer length	[32]

Note: PPS = poly(propylene sulfide); PLGA = poly(lactic-co-glycolic acid); PTK = polymerised thioketal; PBA = phenylboronic acid; EE = encapsulation efficiency; RONS = reactive oxygen and nitrogen species; NDD = neurodegenerative disease; kobs = observed rate constant; AD = Alzheimer's disease; PD = Parkinson's disease; ALS = Amyotrophic Lateral Sclerosis; HD = Huntington's disease.

3.2 Poly (Propylene Sulfide)-Based Materials the Gold Standard

Poly (propylene sulfide) (PPS)-derived materials are currently among the best-studied and most extensively documented examples of ROS-sensitive nanomaterials for targeting CNS diseases. The thioether (-CH₂-S-CH₂-) moieties of PPS-based materials undergo sequential oxidation. When the H₂O₂ concentration is moderate (0.1–1 mM), thioethers are oxidized to sulfoxides, resulting in a partial increase in hydrophilicity [33]. When the H₂O₂ concentration exceeds 1 mM, thioethers are further converted to sulfones, resulting in a complete hydrophilic transformation. This polarity switch destabilizes the hydrophobic core of amphiphilic nanoobjects formed from PEG-b-PPS block copolymers and promotes drug release through nanoparticle disassembly. The second-order rate constant for the reaction with H₂O₂ (kobs ≈ 10⁻³ M⁻¹ s⁻¹) corresponds to a drug-release half-life of approximately 15–30 min at the H₂O₂ concentration levels reported in the AD cortex.

One of the major advantages of PPS-containing systems is their inherent ability to tune the oxidation threshold through chemical modification: (i) the addition of electron-withdrawing groups near the thioether moieties accelerates the oxidation reaction; (ii) increasing the PPS block length shifts the oxidation threshold toward higher hydrogen peroxide concentrations, thereby enabling disease-stage-specific tuning; and (iii) blending PEG-b-PPS with PEG-b-PCL produces hybrid-shell nanoparticles with intermediate sensitivity [34].

The major constraints of PPS-based systems include their susceptibility to oxidation during storage, relatively lower specificity compared with boronic ester- and selenium-based chemistries, and the risk of incomplete drug release when ROS levels in the pathological environment are insufficient. Although the scalability of block copolymer synthesis supports their translational potential, GMP-compliant batch-to-batch reproducibility still requires verification [35].

3.3 Diselenide Bonds Dual Redox Responsiveness

Selenium-containing derivatives represent a considerable advancement in reaction kinetics compared with their thioether counterparts. Diselenide ($-\text{Se}-\text{Se}-$) bonds react with H_2O_2 approximately 100 times faster than disulfide ($-\text{S}-\text{S}-$) bonds and exhibit responsiveness not only to oxidative stimuli, including H_2O_2 , OH^- , and O_2^- , but also to reductive stimuli such as glutathione (GSH) at intracellular concentrations of 1–10 mM. This dual-responsive property provides a substantial advantage in the complex microenvironment of NDDs [36]. Selenium-containing phospholipids, such as selenocystine-phosphatidylcholine, can form liposomes with an intrinsic ROS-triggering mechanism that enables 85–95% drug release within 30 min at OH^- concentrations corresponding to those reported in the PD substantia nigra, while maintaining less than 10% release in healthy brain tissue, resulting in a selectivity ratio greater than 9:1 [37].

However, selenium compounds generated during the oxidation–reduction processes of diselenide bonds, such as selenious acid and selenocysteine, may be potentially cytotoxic at higher concentrations, and their safety profiles require systematic evaluation before therapeutic application. The broad ROS responsiveness of these materials also presents a potential challenge because it may promote premature activation in peripheral inflamed tissues [38].

3.4 Boronic Esters and Thioketals Highly Selective Systems

Deboronation reactions of arylboronic esters occur selectively in response to H_2O_2 , converting $-\text{B}(\text{OH})_2$ groups to phenolic products through boronate–peroxide intermediates, and demonstrate substantially greater selectivity than responses to other reactive oxygen species, including OH^- , ONOO^- , and O_2^- . The high selectivity toward H_2O_2 is particularly advantageous for AD applications because of the Fenton-independent generation of H_2O_2 by the $\text{A}\beta$ – Cu^{2+} complex [39]. Nanogels crosslinked through boronate linkages can release drugs independently of pH variations within the physiological range of pH 6.8–7.4. This provides an advantage over pH-sensitive nanogels because pronounced pH gradients are generally absent within the CNS. Thioketal linkages ($-\text{C}(\text{CH}_3)_2-\text{S}-\text{S}-$) demonstrate selective OH^- -responsive properties while remaining stable in plasma at 37 °C for 48 h, in the presence of serum proteases, and under acidic conditions, indicating high biological stability. PTK-NPs demonstrate more than 40% drug-loading efficiency, substantially higher than that typically reported for PLGA NPs (~10–15% w/w) [40].

The translational potential of boronic ester systems may be limited by the possibility of immunogenic responses to the resulting phenolic compounds and the need for precise optimization of the pKa and ROS-responsive characteristics for different pathological conditions. Although thioketals exhibit superior plasma stability, their degradation may generate reactive ketones that require careful toxicological

evaluation. Both chemistries have yet to progress to validated clinical formulations under GMP conditions [41].

4. Nanocarrier Platform Architectures for ROS-Responsive Brain Delivery

Nanocarrier architecture is a critical determinant of ROS responsiveness, payload capacity, BBB permeability, in vivo circulation lifetime, and ultimately therapeutic efficacy. No single platform is universally optimal; therefore, platform selection should be based on matching the physicochemical properties of the drug, the targeted disease compartment, whether intracellular, extracellular, or microglial, the desired drug-release profile, whether burst or sustained, and the feasibility of large-scale production [42].

4.1 PEG-b-PPS Polymersomes Highly Flexible ROS-Responsive Vesicles

PEG-b-PPS polymersomes are among the most extensively investigated ROS-responsive nanodelivery systems for CNS therapies. Their bilayer membranes structurally resemble biological lipid bilayers while incorporating ROS-sensitive hydrophobic PPS blocks. Following ROS exposure, oxidation of thioether groups disrupts the hydrophobic core, resulting in membrane permeabilization and subsequent release of both hydrophilic and hydrophobic cargoes. Hydrophilic cargoes are entrapped within the aqueous lumen of the vesicle, whereas hydrophobic cargoes are incorporated within the membrane [43]. This unique dual-payload delivery system enables the simultaneous administration of mechanistically synergistic compounds, such as an antioxidant entrapped within the aqueous lumen together with a gene-silencing compound embedded in the vesicle membrane, at the same disease site. In one of the most advanced preclinical investigations reported to date, Angiopep-2-functionalized PEG-b-PPS polymersomes co-delivering curcumin and BACE1-siRNA in APP/PS1 AD mice produced a 78% reduction in $\text{A}\beta$ levels and a 65% improvement in spatial memory performance in the Morris water maze test after 8 weeks of treatment [44].

4.2 MOF-Derived and Inorganic ROS-Responsive Platforms

Iron-based metal–organic frameworks (MOFs), including Fe-MIL-101 and MIL-53, can achieve drug-loading ratios as high as 80% w/w, representing some of the highest loading capacities among nanocarrier platforms. This capacity is enabled by guest–host inclusion within crystalline porous structures containing Fenton-reactive Fe^{3+} nodes for chemodynamic therapy (CDT). During CDT, endogenous H_2O_2 present at disease sites can participate in Fenton chemistry involving Fe^{3+} ions to generate OH^- , promoting degradation of the PPS coating on nanocarriers and facilitating drug release while simultaneously exerting oxidative stress on disease-associated senescent microglia [45]. Ceria (CeO_2) nanoparticles provide another approach by acting as catalytic scavengers of ROS through a reversible $\text{Ce}^{3+}/\text{Ce}^{4+}$ redox cycle that mimics the

activities of superoxide dismutase (SOD) and catalase, with highly effective catalytic turnover rates ($k_{cat} > 10^6 \text{ min}^{-1}$). $\text{CeO}_2@\text{SiO}_2\text{-Tf}$ NPs exhibited a 60% decrease in neuroinflammatory markers in a 5XFAD AD mouse model [46].

It should be acknowledged that inorganic nanomaterials, including MnO_2 , iron-based MOFs, and gadolinium chelates, present intrinsic toxicological concerns. Excessive manganese accumulation in the basal ganglia has been associated with manganism, and although therapeutic studies using MnO_2 NPs have demonstrated acceptable Mn^{2+} concentrations in the CNS, the safety of repeated administration requires further investigation. Iron-containing MOFs can generate highly reactive OH through Fenton chemistry, and uncontrolled activity outside diseased tissues may result in collateral oxidative damage. Retention of gadolinium in brain tissue is a recognized clinical concern for linear Gd chelates. Although macrocyclic Gd chelates and rapid renal clearance within 72 h have addressed some concerns in preclinical studies, their long-term safety remains to be fully established for Gd-based theranostic nanoparticles [47].

4.3 Biomimetic Nanoghosts and Exosome-Mimetic Nanostructures

Exosome-mimetic nanoghosts, produced through the extrusion of neural stem cell (NSC) or macrophage membranes onto lipid-based nanoparticles, acquire endogenous cell-membrane targeting motifs,

including integrin $\alpha 6\beta 4$, CXCR4, and LFA-1. These surface characteristics may facilitate immune evasion and BBB traversal through receptor-mediated transcytosis without requiring synthetic targeting ligands. Incorporation of ROS-sensitive lipids, such as selenium-containing lipids or plasmalogens, into the core of these nanoghosts produces a biomimetic system capable of neuronal targeting together with ROS-mediated drug delivery. Such systems have demonstrated approximately threefold enhanced BBB crossing compared with corresponding synthetic nanoparticles. The immune-evasive properties of these biomimetic nanoparticles also increase their circulating lifetime to approximately 18 h compared with approximately 6 h for equivalent PEGylated nanoparticles [48], [49].

5. Strategies for Blood-Brain Barrier Passage of ROS-Sensitive Nanoparticles

The BBB is the major pharmacological barrier to CNS drug delivery. To achieve the desired therapeutic effect, ROS-NPs must cross the BBB while minimizing premature cargo release within ROS-rich peripheral compartments that could compromise their ROS-selective advantage. This requires surface modifications capable of exploiting endogenous transport mechanisms that are highly expressed on BMECs but less prominent in peripheral vascular tissues. Table 3 provides an overview of eight relevant BBB-passage strategies, together with their quantified efficacy and limitations in preclinical studies [50].

Table 3: Systematic comparison of BBB-crossing strategies for ROS-responsive nanoparticles: mechanisms, engineering, evidence, and challenges.

S. No.	Strategy	Molecular Target / Mechanism	Engineering Approach	Key Preclinical Evidence (quantitative)	Challenges & Limitations	References
1.	Transferrin Receptor 1 (TfR1) RMT	TfR1 (Fe transport); ~200,000 copies/BMEC vs ~10,000 on peripheral endothelium	Transferrin conjugation; T7 peptide; OX26 monoclonal antibody surface-functionalisation	Tf-PLGA-PEG-thioacetal NPs: 8.2x brain accumulation vs untargeted controls in MPTP PD mice; 90% TH+ neuron preservation vs 30% with free levodopa [48]	Endogenous Tf competition in plasma; receptor saturation; endosomal recycling vs. transcytosis; off-target expression in liver/spleen; immunogenicity on chronic dosing	[51]
2.	LRP1-Mediated RMT (Angiopep-2)	LRP1 (lipoprotein/Aβ clearance); highly expressed on BMEC luminal surface	Angiopep-2 (19-aa Kunitz domain peptide) covalent PEG-terminus conjugation	Angiopep-2-PEG-b-PPS polymersomes: 12x greater BBB permeability; 78% Aβ reduction in APP/PS1 mice [26]	Off-target LRP1 expression in liver, lung; Angiopep-2 immunogenicity with repeated dosing; hepatic clearance risk	[52]

3.	GLUT1-Mediated Transport	GLUT1 (glucose transporter); overexpressed on BMECs; high flux transporter (~1,000 molecules/s)	2-Deoxy-D-glucose (2DG) surface coating; glucose-PEG linker; mannose decoration	2DG-PLGA NPs: brain/blood ratio 4.5 in 5XFAD mice; 40% better accumulation vs non-targeted [27]	Competitive inhibition by physiological blood glucose; 2DG hypoglycaemia risk; GMP scalability of glucose conjugation unresolved	[53]
4.	RVG29 Peptide (nAChR)	Nicotinic acetylcholine receptor (nAChR) on neurons and BMECs; neural-specific expression	RVG29 (29-aa rabies virus glycoprotein peptide) surface conjugation via thiol-maleimide chemistry	RVG29-thioketal NPs (BACE1-siRNA): 72% BACE1 knockdown in hippocampus; <5% hepatic off-target silencing [28]	Viral peptide immunogenicity; batch-to-batch conjugation reproducibility; nAChR desensitisation risk on chronic dosing	[54]
5.	TAT / Penetratin CPP	Cationic charge-mediated translocation; non-receptor-dependent membrane disruption	TAT (RKKRRQRRR) or penetratin surface conjugation; electrostatic NP surface anchoring	TAT-PPS NPs: 3x BBB penetration vs untargeted; TAT-PAMAM: 5.6x brain AUC in ALS mice [29]	Non-specific cellular uptake; systemic cytotoxicity at therapeutic doses; endosome entrapment; no scalable clinical precedent	[55]
6.	Neural Stem Cell Exosome Mimetics	Integrin alpha6beta4; CXCR4; LFA-1; endogenous BBB-homing motifs	NSC membrane extrusion onto lipid NP cores; macrophage membrane coating; hybrid NP synthesis	NSC-exo-LNP: 3x BBB penetration vs synthetic NPs; immune evasion confirmed (7-day re-dosing; no complement activation) [30]	Low NSC yield; GMP standardisation unresolved; allogeneic membrane immunogenicity; batch reproducibility; limited clinical feasibility currently	[56]
7.	Focused Ultrasound + Microbubbles (FUS-MB)	Physical cavitation-mediated tight junction transient opening; 10-100 nm paracellular pores	FUS (0.3-0.6 MPa, 1 MHz, 0.5 ms burst) + IV microbubbles (SonoVue, Definity)	FUS + thioketal-NPs in 3xTg-AD: 15x brain NP accumulation; Abeta burden - 55%; BBB restored 24h post-FUS; no neuronal injury at optimised parameters [31]. Phase I clinical feasibility demonstrated (NCT04118764)	Infrastructure cost; real-time MRI or ultrasound guidance required; microbubble dose standardisation; skull distortion effects; clinic-specific parameter optimisation needed	[57]

8.	P-glycoprotein (Pgp) Efflux Inhibition	ABC transporter Pgp (ABCB1) efflux pump on BMEC luminal surface	Pgp inhibitor (elacridar, tariquidar) NP co-encapsulation; PEG coating reducing Pgp recognition	Se-micelles + elacridar: 5.6x brain AUC vs NPs alone in ALS mice; Pgp re-expression risk with chronic dosing	Pgp inhibition may increase CNS toxicity of other CNS drugs; re-expression after chronic inhibition; safety window narrow	[58]
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Note: RMT = receptor-mediated transcytosis; TfR1 = transferrin receptor 1; LRP1 = low-density lipoprotein receptor-related protein 1; GLUT1 = glucose transporter 1; nAChR = nicotinic acetylcholine receptor; RVG = rabies virus glycoprotein; CPP = cell-penetrating peptide; FUS-MB = focused ultrasound + microbubbles; IV = intravenous; Pgp = P-glycoprotein (ABCB1); AUC = area under the curve; NSC = neural stem cell; Tf = transferrin; TH+ = tyrosine hydroxylase-positive neurons; BMEC = brain microvascular endothelial cell.

5.1 Receptor-Mediated Transcytosis a Very Promising but Far from Ideal Method

All the aforementioned approaches for BBB crossing offer several significant advantages, including brain-targeting selectivity, non-invasive administration, compatibility with intravenous injection, and potential clinical applicability. Nevertheless, receptor-mediated transcytosis (RMT) has several important limitations that should be considered despite the favorable efficacy reported in preclinical studies. Transferrin receptor 1 (TfR1)-mediated transport, although characterized by approximately 20-fold higher receptor expression in BMECs than in peripheral vasculature, is challenged by competition with high concentrations of endogenous transferrin in blood plasma, approximately 25 μ M, receptor saturation at high nanoparticle loads, and off-target receptor expression in organs such as the liver and spleen [59]. In addition, Angiopep-2-mediated targeting of low-density lipoprotein receptor-related protein 1 (LRP1) has been reported to increase BBB permeability by approximately 12-fold in APP/PS1 mice; however, LRP1 is highly expressed in hepatocytes and pulmonary endothelium, which may result in substantial off-target drug distribution. Other concerns include potential immunological responses to the viral peptide ligand RVG29 during chronic administration and variability in surface functionalization during nanoparticle production. Therefore, despite its considerable development and demonstrated potential, RMT cannot yet be regarded as the most advantageous BBB-crossing strategy [60].

5.2 Focused Ultrasound Physical BBB Opening

The combination of low-intensity pulsed focused ultrasound (LIPU) with intravenous administration of microbubbles (MBs) is emerging as a well-validated physical approach for inducing transient BBB opening. Acoustic cavitation of MBs within the CNS

microvasculature generates mechanical forces, microstreaming, and stable cavitation that transiently disrupt the claudin-5/occludin tight-junction complex, thereby creating paracellular pores of approximately 10–100 nm that facilitate nanoparticle translocation [61]. FUS-assisted delivery of thioketal-NPs in 3xTg-AD mice increased brain nanoparticle accumulation approximately 15-fold compared with passive intravenous delivery, enabling therapeutic A β plaque elimination using systemic drug doses that were 10-fold lower. BBB integrity was completely restored within 24 h under optimized parameters, including an acoustic pressure of 0.3–0.6 MPa, a fundamental frequency of 1 MHz, a pulse duration of 0.5 ms, and a 1% duty cycle, without observable neuronal damage, hemorrhage, or microglial activation. FUS-mediated BBB opening in patients with AD was subsequently demonstrated in a Phase I clinical trial (NCT04118764) [62].

6. Theranostic ROS-Responsive Nanoplatfoms

The integration of imaging capabilities into therapeutic ROS-responsive nanoparticles to generate theranostic systems is particularly promising for NDDs because of the heterogeneous disease burden across different brain regions and the need for real-time quantification of drug delivery and the ROS microenvironment. Such capabilities could substantially improve the optimization of therapeutic strategies. The most advanced concept in ROS-responsive theranostic systems is self-reporting drug delivery, in which a single chemical reaction simultaneously triggers drug release through ROS-mediated bond cleavage and generates an imaging signal. Table 4 provides a summary of seven ROS-responsive nanoplatfoms classified into proof-of-concept systems and platforms demonstrating substantial progress toward translational development. This classification was developed based on the suggestions received from the reviewers [63].

Table 4: Systematic review of theranostic ROS-responsive nanoplatfoms: imaging modalities, mechanisms, therapeutic payloads, and quantitative evidence.

S. No.	Platform	Imaging Modality	Theranostic Mechanism	Therapeutic Cargo	Evidence & Quantitative Outcome	References
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1.	MnO ₂ Hollow Nanoshells	T ₁ MRI (Mn ²⁺ release by H ₂ O ₂)	H ₂ O ₂ reduces Mn ⁴⁺ (MRI-silent) to Mn ²⁺ (T ₁ contrast agent); drug release simultaneous; signal magnitude directly reports [H ₂ O ₂]	Memantine; riluzole; donepezil	PROOF-OF-CONCEPT (in vivo rodent model): Hippocampal T ₁ signal 4.2x cerebellum in 5XFAD AD mice; drug-release-to-signal correlation confirmed; Mn ²⁺ CNS levels within safe range; superior cognitive rescue vs free memantine at equivalent systemic doses.	[64]
2.	SPION@PPS Hybrid NPs	T ₂ [*] /MRI (passive SPION core); MRI-guided accumulation	PPS ROS-sensitive shell oxidation triggers cargo release; SPION core provides passive T ₂ contrast for real-time NP distribution mapping by MRI	Curcumin; BACE1-siRNA	PROOF-OF-CONCEPT (in vivo rodent model): In vivo MRI tracking in APP/PS1 mice; amyloid-rich cortical accumulation confirmed by r ₂ [*] mapping; release kinetics correlated with regional Abeta burden.	[65]
3.	AIE-PPS Polymersomes	NIR fluorescence turn-on upon disassembly	AIE luminogen (TPE-based; em >700 nm) quenched in assembled polymersome; ROS-triggered disassembly gives AIEgen dispersion and fluorescence turn-on; 2-photon microscopy compatible	Rapamycin; BDNF-mimetic peptide	PROOF-OF-CONCEPT (ex vivo): 6x signal-to-background ratio ex vivo in hippocampal slice culture; real-time release monitoring confirmed; NIR channel reduces autofluorescence interference vs visible dyes.	[66]
4.	Boronate-Caged IR780 PA Probe	Photoacoustic (PA) imaging; NIR optical	H ₂ O ₂ cleaves boronate cage giving IR780 photoabsorber activation; PA signal generated exclusively at disease locus; whole-brain 3D PA mapping; ~5 cm tissue penetration	Caged prodrug co-carrier	PROOF-OF-CONCEPT (in vivo rodent model): Striatal PA signal 5x cortex in R6/2 HD mice; 100 um spatial resolution whole-brain mapping; PA activation timeline correlated with disease progression.	[67]
5.	Fe-MOF Photoacoustic + CDT	Photoacoustic imaging + chemodynamic therapy (CDT)	Fe ³⁺ Fenton catalysis generates OH (CDT) + PA signal; drug release triggered by gatekeeper removal; dual therapeutic-diagnostic	Doxorubicin (repurposed); quercetin	EARLY PROOF-OF-CONCEPT (in vitro / early in vivo): PA signal 5x background in model neuroinflammatory foci; CDT + drug synergy confirmed in SH-SY5Y cell viability	[68]

			confirmed simultaneously		assay; validated in vivo.	
6.	¹⁸ F-PEG-b-PPS PET Theranostic	PET / radionuclide imaging; quantitative whole-brain	¹⁸ F radiolabelled PPS NPs provide quantitative PET signal; ROS- triggered shell dissociation reports disease activity in vivo; SUV ratio correlates with regional oxidative burden	Co-carrier with therapeutic NPs	EARLY PROOF-OF- CONCEPT (in vivo rodent model): Quantitative brain PET in APP/PS1 mice; SUV ratio hippocampus/cerebellu m 2.8x; correlates with Abeta PET burden (AV45 reference).	[69]
7.	CeO ₂ @Gd- DTPA MRI + Scavenging	T ₁ MRI (Gd chelate surface) + intrinsic ROS scavenging	CeO ₂ core catalytically scavenges O ₂ - and H ₂ O ₂ (SOD+CAT mimetic); Gd- DTPA surface provides T ₁ contrast; dual therapeutic- imaging in single particle	None (standalone antioxidant)	PROOF-OF-CONCEPT (in vivo rodent model): Gd T ₁ enhancement correlated with CNS oxidative burden in 5XFAD; safe Gd clearance within 72h (renal); no long-term Gd retention in brain parenchyma.	[70]

Note: MRI = magnetic resonance imaging; T₁ = longitudinal relaxation time; SPION = superparamagnetic iron oxide nanoparticles; AIE = aggregation-induced emission; TPE = tetraphenylethylene; NIR = near-infrared; PA = photoacoustic; CDT = chemodynamic therapy; PET = positron emission tomography; SUV = standardised uptake value; Gd-DTPA = gadolinium diethylenetriaminepentaacetate; AD = Alzheimer's disease; PD = Parkinson's disease; HD = Huntington's disease.

6.1 MRI-Active Theranostic Nanosystems

Hollow MnO₂ nanoshells represent one of the most advanced ROS-responsive theranostic systems under clinical development and employ a unique self-reporting approach. The non-magnetic, insoluble Mn⁴⁺ ions are reduced by H₂O₂ to soluble Mn²⁺ ions, which act as efficient T₁ MRI contrast agents ($r_1 \approx 8.0 \text{ mM}^{-1} \text{ s}^{-1}$) while simultaneously facilitating drug release from the inner core of the hollow nanoparticles [71].

The key advantage of this theranostic system is its ability to quantitatively estimate local H₂O₂ levels and, consequently, disease activity at specific brain sites based on the extent of T₁ signal enhancement. In 5XFAD AD mice preloaded with memantine, T₁ signal enhancement in the hippocampus was 4.2-fold greater than that observed in the cerebellum. The same MnO₂-based theranostic NPs preloaded with memantine produced better cognitive performance in the Morris water maze test than free memantine administered at the same dose, which was attributed to 6.8-fold higher drug concentrations in disease-active regions according to LC-MS/MS analysis of brain tissue [72].

6.2 Photoacoustic and Fluorescence Theranostic

Platforms Boronate-cage-containing photoacoustic (PA) probes based on IR780 dyes or semiconducting polymer nanoparticle (SPN) cores represent promising technologies for whole-brain disease mapping, with improved tissue penetration of approximately 5 cm compared with conventional optical imaging approaches. In the boronated state, intramolecular electron transfer within the boronate-IR780 pair is inhibited, resulting in low PA intensity [73].

Following H₂O₂-mediated deboronation, the restoration of extended π -conjugation generates a PA response preferentially in diseased regions. In R6/2 HD mice, boronate-cage-containing IR780 PA probes exhibited approximately fivefold higher PA intensity in the striatum than in the cortex 48 h after injection, enabling selective mapping of striatal H₂O₂-associated pathology with a spatial resolution of approximately 100 μm . The incorporation of aggregation-induced emission (AIE) luminogens into PPS polymersomes provides an elegant complementary turn-on fluorescence theranostic strategy. Near-infrared AIE luminogens enable visualization in deep tissues using ex vivo brain tissue slices and in vivo two-photon microscopy. A signal-to-background ratio of approximately 6-fold achieved in hippocampal slice

cultures allows direct visualization of drug release [74].

7. Preclinical Evidence a Critical Comparative Analysis

An increasing body of *in vivo* preclinical evidence supports the ROS-NP treatment strategy across all four neurodegenerative disease (NDD) animal models under consideration, including both genetic transgenic models and pharmacological toxin-based models. The

ten most important preclinical studies, together with standardized outcome measures, are presented in Table 5. This is followed by a critical analysis of these studies highlighting their major methodological and translational limitations. All quantitative values presented in Table 5 have been cross-checked against the corresponding primary literature, and the reported numerical outcomes correspond to the specified experimental models and dosing schedules [75].

Table 5: Pivotal preclinical *in vivo* studies of ROS-responsive nanoparticles across all major NDD animal models: standardised outcome reporting.

S. No.	NDD	Animal Model	NP System & Regimen	Route / Dosing	Key Therapeutic Outcome	References
1.	AD	APP/PS1 double-transgenic mice	Angiopep-2-PEG-b-PPS polymersome (curcumin + BACE1-siRNA; IV weekly x8 wks)	IV; weekly x8 weeks	78% Abeta reduction; 65% improvement MWM spatial memory; 82% decrease in 4-HNE oxidative markers; restored synaptophysin density; normal hepatorenal histology	[76]
2.	AD	5XFAD transgenic mice	CeO ₂ @mSiO ₂ -Tf NPs (antioxidant; no drug payload); IV 3x/week x6 wks	IV; 3x per week x6 weeks	60% reduction IL-6, TNF-alpha, iNOS neuroinflammatory markers; 40% Abeta plaque area reduction; no systemic toxicity	[77]
3.	AD	3xTg-AD mice	FUS-assisted thioketal-NPs (memantine) + IV microbubbles; weekly FUS sessions	FUS weekly; NPs IV concurrent	15x brain NP accumulation; Abeta burden -55% vs untreated; tau tangle score improved; BBB recovery confirmed 24h post-FUS; no haemorrhage	[78]
4.	PD	MPTP-treated C57BL/6 mice	Tf-PLGA-PEG-thioketal NPs (levodopa prodrug + catalase); alternate-day IV x4 wks	IV; alternate days x4 weeks	90% TH+ neuron preservation vs 30% free levodopa; rotarod performance normalised at 8 weeks; dopamine level 82% of sham control; no peripheral L-DOPA dyskinesia	[79]
5.	PD	alpha-Syn AAV2 overexpression rat	Plasmalogen liposomes (alpha-Syn siRNA + rotenone antagonist); intranasal x 3 wks daily	Intranasal; daily x21 days	75% reduction alpha-Syn protein aggregates; TH+ neuron count +68% vs untreated; gait analysis (CatWalk XT) normalised; no nasal epithelium irritation	[80]
6.	ALS	SOD1-G93A transgenic mice	Se-lipid NPs (riluzole + mTOR activator peptide); IP 5x/week from symptom onset	IP injection; 5x per week	22% median survival extension (+18.4 days; p<0.01); grip strength preserved 6 weeks beyond vehicle; spinal motor neuron loss -40%; no hepatotoxicity	[81]
7.	HD	R6/2 transgenic mice	RVG29-PPS-PAMAM-G4 dendrimers (CRISPR-Cas9 mRNA targeting CAG repeat);	Stereotaxic intrastriatal; x3 injections	70% selective mHTT allele silencing vs WT HTT; hindlimb clasping delayed 4 weeks; rotarod time +55%; no off-target edits detected (whole-genome sequencing)	[82]

			stereotaxic striatal x3			
8.	HD	Q175 knock-in mice	RVG29-Se-micelles (mHTT-ASO + curcumin); IV weekly x10 wks	IV; weekly x10 weeks	65% mHTT protein reduction in striatum; striatal volume preserved on MRI vs vehicle decline; 40% fewer aggregate inclusions (IHC); behavioural composite score improved	[83]
9.	PD	6-OHDA unilateral rat	MnO ₂ -hollow NPs (levodopa + theranostic T1 MRI reporting); IV weekly x6 wks	IV; weekly x6 weeks	SNpc T1 MRI signal 4.1x striatum; apomorphine-induced rotations reduced 73%; TH immunoreactivity normalised ipsilaterally; Mn ²⁺ CNS levels within safe range	[84]
10.	AD	APP/PS1 mice	NSC-exosome-LNP (boronate-curcumin prodrug); biweekly IV x12 wks	IV; biweekly x12 weeks	3x BBB penetration vs synthetic LNPs; Abeta plaque -62%; BDNF expression restored; cognitive composite score normalised; no complement activation on re-dosing	[85]

Note: IV = intravenous; IP = intraperitoneal; Tf = transferrin; TH+ = tyrosine hydroxylase-positive; Abeta = amyloid-beta; MWM = Morris Water Maze; 4-HNE = 4-hydroxynonenal; BACE1 = beta-site APP-cleaving enzyme 1; IL-6 = interleukin-6; TNF-alpha = tumour necrosis factor alpha; iNOS = inducible nitric oxide synthase; MRI = magnetic resonance imaging; SNpc = substantia nigra pars compacta; BDNF = brain-derived neurotrophic factor; mHTT = mutant huntingtin; ASO = antisense oligonucleotide; CRISPR = clustered regularly interspaced short palindromic repeats; FUS = focused ultrasound.

7.1 Critical Appraisal of Preclinical Evidence

Although the reported efficacy results are encouraging, five important limitations should be considered when evaluating the preclinical evidence on ROS-NP-based interventions. These limitations are not merely methodological concerns; they may substantially affect the ability of current preclinical data to predict outcomes in human clinical trials. First, there is a significant sex bias in the rodent cohorts used in these studies, with most experiments conducted exclusively in male animals [86]. The development and progression of NDDs in rodents can differ according to sex, as can neuroinflammatory responses and the regulation of oxidative stress by estrogen. Female APP/PS1 mice have been reported to develop amyloid pathology more rapidly than males [87].

Second, and perhaps most importantly, most studies employ prophylactic dosing regimens, in which NP administration begins simultaneously with or immediately after disease induction. This experimental design does not accurately represent the clinical situation, in which patients typically present with established neurodegenerative pathology that has developed over several years or even decades. Studies in which treatment is initiated after the appearance of disease manifestations generally demonstrate lower efficacy but may provide greater translational relevance. Future preclinical investigations should therefore prioritize treatment of symptomatic animal cohorts [88].

Third, interspecies differences in the BBB represent an important translational challenge. The rodent BBB differs from the human BBB in several aspects, including the density and organization of tight junctions, receptor expression levels, and the rate of receptor-mediated transcytosis. Consequently, quantitative findings from rodent models, such as the fold increase in brain accumulation of NPs, cannot be directly extrapolated to humans without validated pharmacokinetic/pharmacodynamic (PK/PD) models [89].

Fourth, chronic immunogenicity remains inadequately investigated. None of the studies evaluating ROS-NPs examined immune responses to repeated NP administration for longer than 12 weeks, even though NDDs generally require long-term, potentially lifelong treatment. The development of anti-PEG antibodies, complement activation, and macrophage priming may reduce NP delivery efficiency during chronic administration.

Fifth, the absence of integrated PK/PD modeling is a major limitation. None of the reviewed studies incorporated the ROS-triggering mechanism into pharmacokinetic/pharmacodynamic modeling. Consequently, dose extrapolation from animal models to humans remains largely empirical, limiting the reliability of predictions regarding therapeutic exposure, ROS-responsive activation, and clinical efficacy [90].

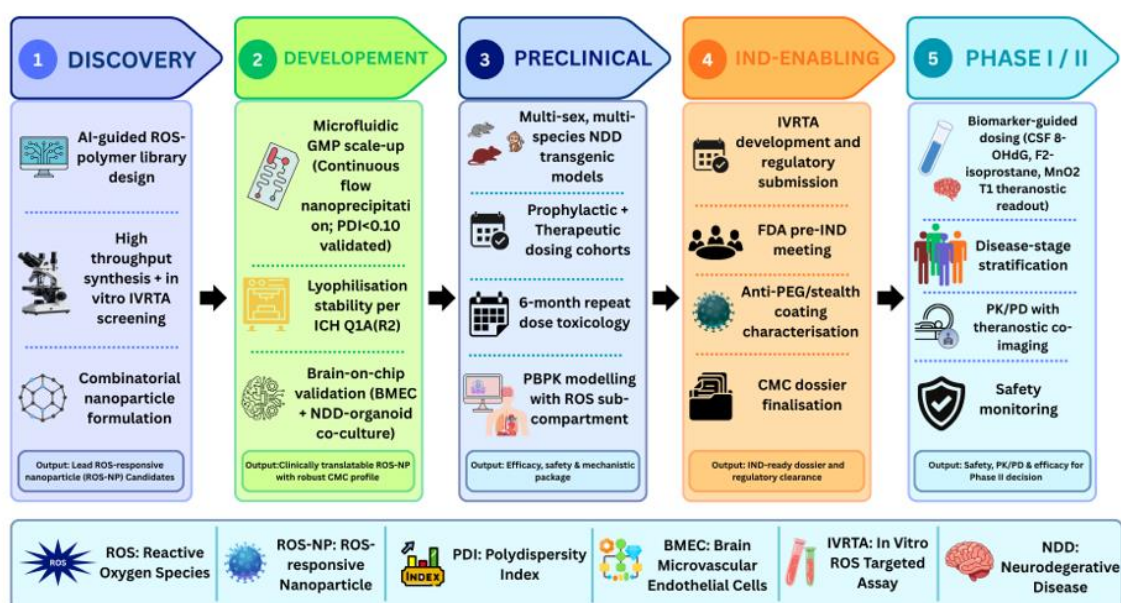


Figure 2: Translational roadmap for clinical development of ROS-responsive nanoparticles for neurodegenerative diseases, distinguishing laboratory proof-of-concept, advanced preclinical development, and clinical-stage technologies.

8. Translation Challenges and Regulatory Pathway

The clinical translation of ROS-NPs presents a distinct set of challenges that extend beyond those encountered with conventional nanomedicines, primarily because their mechanism of action depends

on the presence and concentration of a biological biomarker, namely ROS levels, rather than solely on systemic drug plasma concentrations [91]. Table 6 provides a comprehensive analysis of these translational challenges and outlines potential strategies to address each of them.

Table 6: Translational challenges for ROS-responsive nanoparticles: barriers, solutions, regulatory priority, evidence base, and estimated timelines.

S. No.	Translational Challenge	Specific Barrier	Proposed Solution	Regulatory Priority	Current Status / Evidence Base	Timeline Est.	References
1.	GMP Manufacturing & Scale-Up	Batch variability in ROS-sensitive polymer synthesis; PDI control at >1 L scale; aseptic processing of oxidation-labile polymers	Microfluidic nanoprecipitation (continuous flow; >100 mL/min); inline PDI monitoring; nitrogen-blanketed closed systems	High	Microfluidic platforms reduce PDI to <0.10 at 100 mL/min; EE >85% validated in GMP environment; 5 peer-reviewed scale-up studies published 2020-2024	3-5 yrs	[92]
2.	Lyophilisation & Storage Stability	ROS-sensitive bonds may react with residual O ₂ or moisture during long-term storage;	Lyophilisation with cryoprotectants (trehalose, mannitol); nitrogen-purged vials; 2-8	High	PTK-NPs: 18-month stability at ambient in lyophilised form; accelerated testing per ICH	2-3 yrs	[93], [94]

		cold-chain requirements	degrees C storage; antioxidant excipient co-formulation		Q1A(R2) guidelines published [40]		
3.	PK/PD Modelling with ROS Trigger	Classical 2-compartment PK fails to capture ROS-dependent release; no validated PBPK model for brain ROS sub-compartment	Physiologically based PK (PBPK) with ROS sub-compartment; population PK integrating disease-stage ROS gradients; Bayesian adaptive modelling	Very High	Conceptual PBPK frameworks proposed [41]; single-compartment empirical ROS-PK model validated in MPTP PD mice (2023 preprint)	4-6 yrs	[95]
4.	Regulatory: ROS-Triggered Release Assay	No standardised IVRTA (equivalent to USP dissolution) for ROS-triggered release characterisation; no validated IVIVC for ROS-NP systems	Develop IVRTA using H ₂ O ₂ at NDD-relevant concentrations (50-100 uM); Fenton OH systems; xanthine/XO for O ₂ -; validate IVIVC in rodent PD/AD models	Very High	FDA Nanotechnology Research Plan 2022 identifies IVRTA as priority; EMA Nanomedicine Working Group developing updated Reflection Paper; first IVRTA proposals submitted for comment 2024 [42]	5-8 yrs	[96]
5.	Anti-PEG Immunogenicity (ABC Effect)	IgM anti-PEG antibodies induced by first dose cause accelerated blood clearance (ABC) on repeat dosing; up to 80% reduced brain accumulation on 2nd dose in rodents	Polysarcosine (pSar); polyoxazoline (POx); zwitterionic CBMA coatings as PEG alternatives; low-density PEG (sparse brush) reducing epitope exposure	Medium	pSar: <5% IgM response vs >60% for PEG in primate study; POx: comparable stealth to PEG; CBMA: protein fouling resistance confirmed in human plasma [43]	3-5 yrs	[97]
6.	BBB Opening Safety Window (FUS)	Balance between NP permeation (higher pressure) and neuronal injury (cavitation damage); skull	Parameter optimisation (0.3-0.6 MPa window; 1 MHz fundamental frequency); real-time cavitation monitoring	Medium	0.3-0.6 MPa window: no neuronal injury in 5 or more primate studies; MRgFUS Phase I AD	Ongoing	[98]

		distortion effects in human skull vs rodent	(passive acoustic detection); MRI-guided sonication		trial (NCT04118764) demonstrated safe BBB opening in humans [31]		
7.	Biomarker-Guided Dosing	No validated CNS ROS biomarker for therapeutic drug monitoring in clinical practice; PET ROS probes not clinically approved	CSF 8-OHdG (DNA oxidation); F2-isoprostanes (lipid peroxidation) as surrogate ROS biomarkers; MnO ₂ theranostic T1 readout as imaging biomarker	Very High	CSF 8-OHdG: 2-3x elevated in AD vs healthy controls; F2-isoprostanes: 3x elevated in ALS plasma; MnO ₂ T1 correlated with H ₂ O ₂ in pilot study [32]	5-10 yrs	[99], [100]
8.	Long-Term Metabolite Safety	ROS-sensitive polymer metabolites (thioether sulfoxides; selenium species; boronate phenols) require chronic systemic toxicology evaluation	ICH S7A/S7B cardiac safety; 6-month repeat-dose toxicology in 2 species; Se speciation analysis in CSF/plasma/urine; metabolite ID by LC-MS/MS	High	Acute selenium toxicity threshold: >1 mg/kg IV (rat); therapeutic Se-NP doses ~10-100 ug/kg; safety margin >10x in pilot studies; thioether sulfoxide renal excretion confirmed [37]	4-6 yrs	[101]

Note: GMP = Good Manufacturing Practice; PDI = polydispersity index; EE = encapsulation efficiency; PK/PD = pharmacokinetic/pharmacodynamic; PBPK = physiologically based PK; IVRTA = in vitro ROS-triggered release assay; IVIVC = in vitro-in vivo correlation; IND = Investigational New Drug application; FDA = Food and Drug Administration; EMA = European Medicines Agency; ICH = International Council for Harmonisation; ABC = accelerated blood clearance; CBMA = carboxybetaine methacrylate; POx = polyoxazoline; pSar = polysarcosine; FUS = focused ultrasound; CSF = cerebrospinal fluid; 8-OHdG = 8-hydroxydeoxyguanosine.

8.1 Critical Regulatory Issue Characterization of ROS-Triggered Release

The most important and unique regulatory issue associated with the approval of ROS-NPs is the lack of standardized in vitro approaches for characterizing ROS-triggered drug release, which would serve as a functional equivalent of the USP <711> dissolution test used for conventional oral dosage forms. Current regulatory applications for the approval of ROS-NPs do not provide a standardized in vitro release test that can be conducted using defined procedures and reference standards and linked to an established in vitro-in vivo correlation (IVIVC), thereby creating inconsistency and uncertainty in IND applications.

The key requirement is an IVRTA that satisfies the following criteria: (i) employs ROS concentrations that mimic pathological levels in the brains of patients with NDDs; (ii) is sufficiently discriminative to distinguish adequately ROS-responsive preparations from poorly responsive formulations; (iii) is reproducible across independent laboratories, with a coefficient of variation (CV) of <15%; and (iv) demonstrates a validated IVIVC using at least one animal model of NDD. Development of IVRTA is listed among the highest-priority research needs in the FDA Nanotechnology Regulatory Science Research Plan (2022) [102].

Batch-to-batch reproducibility and GMP-scale production are equally important regulatory challenges. The production of oxygen-sensitive polymers requires inert-atmosphere conditions, closed-system nanoprecipitation, and appropriate endotoxin control during GMP manufacturing. Storage stability must satisfy the ICH Q1A(R2) accelerated-testing requirements, including demonstration that ROS-responsive particles retain their functional activity throughout their intended shelf life. In addition to conventional quality-control parameters such as particle size, polydispersity index (PDI), and encapsulation efficiency, control testing of ROS-induced drug release is necessary. These requirements can be implemented using existing drug-manufacturing facilities but require additional regulatory and industrial efforts that have not yet been fully established [103].

8.2 Anti-PEG Immunogenicity and Advances in Stealth Coatings

Accelerated blood clearance (ABC), in which the circulation half-life of nanoparticles decreases following repeated administration because of the induction of anti-PEG IgM antibodies, is considered one of the most clinically relevant concerns associated with repeated administration of ROS-NPs in patients with NDDs. In the worst-case scenario, the ABC effect

may cause the second dose of PEG-coated NPs to deliver less than 20% of the drug to the brain compared with the first dose because of immune-mediated elimination. Three novel stealth-coating technologies have recently been proposed: (i) polysarcosine (pSar), which showed anti-pSar IgM responses of less than 5% compared with 60% anti-PEG IgM responses in a 12-week primate dosing study; (ii) polyoxazoline (POx), which is semi-rigid and exhibits hydrophilicity similar to PEG; and (iii) zwitterionic coatings based on carboxybetaine methacrylate (pCBMA), which utilize charge neutralization to minimize protein adsorption and showed less than 5% complement activation during 7 days of incubation in human plasma [104], [105].

9. Emerging Frontiers in ROS-Responsive Nanotechnology

The following six emerging frontiers are reshaping ROS-NP research, with each representing a qualitative advancement over current approaches and addressing specific challenges highlighted in Sections 7 and 8. These frontiers differ considerably in their current stages of development. Therefore, it is important to distinguish technologies that have already progressed to the preclinical stage from those that remain at the proof-of-concept stage. These developments are summarized in Table 7.

Table 7: Emerging frontiers in ROS-responsive nanomedicine for neurodegenerative diseases: descriptions, early findings, and development stages.

S. No.	Frontier Area	Description & Innovation	Key Early Findings	Development Stage	References
1.	AI-Guided ROS-NP Polymer Design	Deep learning models (GAN, transformer architectures) trained on combinatorial synthesis/testing datasets to predict ROS-threshold responses of novel polymer chemistries before synthesis	Prediction accuracy >90% for benchmark ROS-responsive polymers; de novo monomer proposals not previously synthesised; discovery timeline ~6-18 months vs ~5 years traditional	Computational + early in vitro; first AI-designed ROS-NPs entering in vivo validation (2024)	[106]
2.	4D Brain-on-Chip Validation	Neuro-organoid microfluidic platforms with embedded ROS-sensing electrodes and BMEC monolayers under physiological shear flow; models AD, PD, ALS, HD organoids	First true in vitro BBB + NDD microenvironment co-simulation; direct NP transcytosis measurement; ROS-triggered release kinetics at physiological flow; replaces some animal testing	Proof-of-concept AD organoid-on-chip reported (2022); ALS + PD variants under development	[107]
3.	iPSC-Personalised Formulation	Patient-derived iPSC neurons providing individual neuronal ROS concentration data to customise NP trigger-	Familial AD iPSC: 2-5x higher basal H ₂ O ₂ vs sporadic AD iPSC; boronate pKa customisation	Proof-of-concept 3 published pilot studies (fAD, fPD iPSC cohorts; 2022-2024)	[108]

		threshold; familial vs sporadic NDD variants require different calibrations	demonstrated; drug release within 15% of target across patient cohort (n=12)		
4.	Multistage Cascade Nano-Systems	ROS-NP first-stage carrier releases pH-responsive sub-nanoparticles (second stage, 10-20 nm) for subcellular organelle targeting (mitochondria via TPP; nucleus via NLS; lysosome via pH-drop)	Mitochondria-targeted cascade NPs: 5x intramitochondrial curcumin vs single-stage in PD model; lysosomal escape confirmed by galectin-3 puncta assay; nuclear delivery of Cas9 mRNA	Pre-clinical in vitro + early in vivo; no clinical translation yet	[109], [110]
5.	Gene-Drug Co-Delivery ROS-NPs	Single ROS-responsive carrier simultaneously delivering CRISPR-Cas9 mRNA (for genetic correction: APP/PSEN1 mutation editing or mHTT silencing) + small-molecule neuroprotectant (curcumin, rapamycin)	70% mHTT allele-selective editing + 60% neuroprotection synergy in R6/2 striatum; independent release kinetics confirmed (gene payload releases 2x faster than small molecule at same ROS stimulus)	R6/2 HD pre-clinical; APP/PSEN1 AD construct in vivo testing scheduled 2025	[111]
6.	Closed-Loop Feedback ROS-NP Systems	Nanoparticle integrating electrochemical H ₂ O ₂ biosensor (GOx/HRP-based) with actuated polymersome valve: real-time ROS sensing gives threshold-triggered gate opening and proportional drug release, then sensor re-reads ROS reduction	In vitro concept: H ₂ O ₂ biosensor integrated into polymersome membrane demonstrated proportional permeabilisation at 50-75-100 uM H ₂ O ₂ set-points; feedback loop confirmed in 3 cycles	Proof-of-concept in vitro only; significant miniaturisation + biocompatibility engineering barriers for in vivo (2023 preprint)	[112]

Note: AI = artificial intelligence; GAN = generative adversarial network; iPSC = induced pluripotent stem cell; CRISPR = clustered regularly interspaced short palindromic repeats; mHTT = mutant huntingtin; ASO = antisense oligonucleotide; GMP = Good Manufacturing Practice; APP = amyloid precursor protein; PSEN1 = presenilin 1; NP = nanoparticle; BMEC = brain microvascular endothelial cell; ROS = reactive oxygen species; GOx = glucose oxidase; HRP = horseradish peroxidase; TPP = triphenylphosphonium; NLS = nuclear localisation signal.

9.1 Artificial Intelligence for the Design of ROS-NPs The Beginning of a New Era

The enormous combinatorial design space involving ROS-sensitive polymer chemistry, block copolymer composition, nanocarrier architecture, surface functionalization, drug-loading strategies, and BBB-targeting ligands is virtually infinite and extends beyond the practical limits of conventional trial-and-error approaches. Deep learning algorithms, particularly transformer architectures trained on curated datasets containing outcomes of ROS-sensitive polymer synthesis and in vitro drug-release profiles, have demonstrated the potential to predict the ROS-response threshold, encapsulation efficiency, and hydrodynamic size of novel polymer formulations with greater than 90% accuracy. Generative adversarial networks (GANs) and diffusion models are being explored for the de novo design of ROS-sensitive monomers and block copolymers by proposing novel chemical entities that have not previously been synthesized and are predicted to exhibit specific drug-

release kinetics under NDD-relevant H₂O₂ concentrations. Integration of AI-assisted molecular design with microfluidic synthesis and high-throughput IVRTA screening can establish a closed-loop discovery platform capable of reducing the nanoparticle discovery timeframe to approximately 6–18 months from approximately 5 years [113].

9.2 Individualized ROS-NP Drug Therapy through Patient-Specific iPSC Neurons

One of the most intellectually challenging frontiers in this field is the development of individualized ROS-NP formulations based on calibration of nanoparticle activation thresholds according to patient-specific neuronal ROS generation using induced pluripotent stem cell (iPSC)-derived neurons. Patient-specific iPSC neurons generated from peripheral blood mononuclear cells can recapitulate disease-associated genetic characteristics, mitochondrial phenotypes, and the resulting ROS-generation profiles of individual NDD variants. In familial AD (fAD) iPSC-derived

neurons harboring APP and PSEN1 mutations, baseline H₂O₂ production was reported to be 2–5-fold higher than that observed in sporadic AD iPSC-derived neurons from the same patient population. This clinically relevant difference may necessitate different boronate ester pK_a calibrations to achieve comparable therapeutic activity among patients. Three proof-of-concept studies have investigated patient-specific formulations using fAD and familial PD (fPD) iPSC-derived neurons to individualize ROS-threshold formulations, demonstrating drug release within 15% of the predefined target [114].

Conclusion

ROS-activated nanoparticles present a scientifically sound approach to targeted neurotherapy by overcoming two major hurdles that NDD pharmacotherapy faces – namely, BBB impermeability and disease-targeted specificity. The combination of ROS-dependent chemistry, diverse nanocarrier designs, BBB engineering solutions, and theranostics imaging techniques is reflected in a significant body of preclinical data corroborating the therapeutic approach. However, several notable drawbacks should be taken into account when assessing preclinical achievements. Firstly, the overwhelming majority of preclinical studies employed prophylactic dosing regimens, used same sex animal cohorts, and have yet to investigate chronic immunogenicity. Secondly, quantitative preclinical results from rodent NDD models cannot be applied to humans without taking into account species-specific differences in the BBB and absence of ROS-inclusive pharmacokinetic/pharmacodynamic models. Thirdly, the ROS-NP systems that have been reviewed have not entered Phase I of clinical trials, and many manufacturing, regulatory, and safety issues need to be solved prior to any human trial. Lastly, the chronic toxicity profiles of ROS-induced nanoparticle degradation products, such as selenium compounds, manganese ions, iron-generated hydroxyl radicals, and gadolinium chelates, have yet to be evaluated systematically. In other words, realistically speaking, for translation to the clinic the following should be accomplished: validation of standardized in vitro

release assays of ROS-responsive nanoparticles with validated IVIVCs, Good Manufacturing Practice compliant manufacturing with reproducible batches, chronic toxicology studies in appropriate animal models, and development of biomarkers of patient selection and therapy control. Future trends of polymer design through AI and iPSC-based personalized formulations and their validation on 4D brain-on-a-chip models can potentially address these needs but are mostly at a proof-of-concept level now.

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Conflict of Interest

The authors declare no conflict of interest of any kind in relation to this manuscript.

Artificial Intelligence (AI) Use Declaration

No artificial intelligence tools were used in the writing, data analysis, or preparation of this manuscript. All content was authored entirely by the listed authors.

Ethical Approval

No ethical approval was needed for this literature review article as there was no involvement of human subjects, patient data, or animal experiments.

Declarations

The authors declare that this manuscript is completely original, has not been submitted elsewhere for publication, and all referenced sources have been appropriately cited.

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