REVIEW

Exosomes as Biomarkers and Therapeutic Agents in Neurodegenerative Diseases: Current Insights and Future Directions

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Abstract

Neurodegenerative diseases (NDs) like Alzheimer's, Parkinson's, and ALS rank among the most challenging global health issues, marked by substantial obstacles in early diagnosis and effective treatment. Current diagnostic techniques frequently demonstrate inadequate sensitivity and specificity, whilst conventional treatment strategies encounter challenges related to restricted bioavailability and insufficient blood–brain barrier (BBB) permeability. Recently, exosomes—nanoscale vesicles packed with proteins, RNAs, and lipids—have emerged as promising agents with the potential to reshape diagnostic and therapeutic approaches to these diseases. Unlike conventional drug carriers, they naturally traverse the BBB and can deliver bioactive molecules to affected neural cells. Their molecular cargo can influence cell signaling, reduce neuroinflammation, and potentially slow neurodegenerative progression. Moreover, exosomes serve as non-invasive biomarkers, enabling early and precise diagnosis while allowing real-time disease monitoring. Additionally, engineered exosomes, loaded with therapeutic molecules, enhance this capability by targeting diseased neurons and overcoming conventional treatment barriers. By offering enhanced specificity, reduced immunogenicity, and an ability to bypass physiological limitations, exosome-based strategies present a transformative advantage over existing diagnostic and therapeutic approaches. This review examines the multifaceted role of exosomes in NDDs, emphasizing their diagnostic capabilities, intrinsic therapeutic functions, and transformative potential as advanced treatment vehicles.

Keywords Exosomes · Neurodegenerative diseases · Biomarkers · Therapeutic agents · Blood–brain barrier · Alzheimer's disease · Parkinson's disease · ALS

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Abbreviations

Aβ	Amyloid-beta
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
ApoBDs	Apoptotic bodies
ASC	Adipose-derived stem cell
AUC	Area under the curve
BBB	Blood-brain barrier
CNS	Central nervous system
CSF	Cerebrospinal fluid
EVs	Extracellular vesicles
FTLD	Frontotemporal lobar degeneration
HD	Huntington's disease
HUC-MSCs	Human umbilical cord mesenchymal stem cells
MS	Multiple sclerosis
MSCs	Mesenchymal stem cells
MVB	Multivesicular body
NDDs	Neurodegenerative diseases
PD	Parkinson's disease

RVG   Rabies virus glycoprotein
SCA   Spinocerebellar ataxia
SMA   Spinal muscular atrophy

Introduction

Neurodegenerative diseases (NDDs) are characterized by the progressive degeneration or death of neurons, which typically do not regenerate or undergo cell cycle completion [1]. As a result, neuronal loss in these disorders is irreversible, often leading to chronic and progressively worsening conditions. While the precise etiology of NDDs remains unclear [2], various risk factors have been implicated, including genetic predispositions, environmental influences, aging, and gene mutations [3]. Neuronal loss in NDDs is frequently associated with metabolic dysfunction or exposure to toxic agents [2], both of which trigger the activation of the innate immune system—a hallmark of many neurodegenerative conditions [4]. A key pathological feature common to most NDDs is the accumulation of misfolded protein aggregates, which serve as histological hallmarks of specific diseases and may overlap across multiple NDDs [5]. These aggregates, which form within neurons, are capable of propagating from affected cells to healthy neurons, contributing to the progression of neurodegeneration [5]. Prominent examples of neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), frontotemporal lobar degeneration (FTLD), amyotrophic lateral sclerosis (ALS), spinocerebellar ataxias (SCA), and multiple sclerosis (MS), each distinguished by unique pathological features but often sharing common mechanisms of neuronal dysfunction and degeneration [6].

As the global population continues to age, with the proportion of individuals over the age of 65 being significant in 2019 and expected to nearly double by 2050, the prevalence of neurodegenerative diseases is projected to rise, emphasizing the need for research into their underlying mechanisms and potential therapeutic strategies [7]. Conventional diagnostic and therapeutic approaches to NDDs have considerable limitations. Biomarker-based diagnostics, such as cerebrospinal fluid (CSF) analysis and positron emission tomography (PET), sometimes involve invasive procedures and may be insensitive in early illness identification [8]. Pharmacological approaches, including as small-molecule medicines, enzyme inhibitors, and monoclonal antibody therapy (e.g., aducanumab), have been developed to target major pathological characteristics like amyloid-beta (Aβ) plaques in Alzheimer's disease [9]. However, these techniques have limited selectivity, inferior effectiveness, and issues with BBB penetration, limiting their therapeutic potential. Furthermore, antibody-based therapies may elicit immunological responses, but their long-term efficacy is questionable due to varying patient responses and associated side effects [10].

In contrast, exosomes provide a revolutionary technique that solves several of these constraints. As naturally occurring extracellular vesicles, they provide a minimally invasive option for biomarker identification, with the possibility for real-time monitoring of disease development via liquid biopsies [11]. Furthermore, exosome-based treatments have a distinct advantage over synthetic drug carriers and viral vectors because they ensure targeted distribution of bioactive compounds with low immunogenicity. Exosomes generated from stem cells have shown neuroprotective capabilities, including regulating neuroinflammation, boosting synaptic plasticity, and improving Aβ clearance [12]. These processes go beyond the direct Aβ-targeting actions of monoclonal antibodies. Furthermore, exosome-mediated drug delivery enables the encapsulation of therapeutic molecules such as RNA-based medicines and neurotrophic factors, increasing bioavailability while limiting off-target effects [13]. These qualities establish exosomes as a paradigm-shifting tool in neurodegenerative disease research, overcoming current gaps in both early detection and treatment efficacy [14].

Exosomes are a subset of extracellular vesicles (EVs) that play a critical role in intercellular communication. Three main types of EVs exist: exosomes, apoptotic bodies (ApoBDs), and microvesicles (MVs), which differ in size and biogenesis [15]. Among these, exosomes are smallest, typically ranging from 30 to 150 nm in diameter, while ApoBDs vary between 50 and 5000 nm, and MVs range from 100 to 1000 nm [16]. The biogenesis of these vesicles follows distinct pathways. Unlike MVs, which bud directly from the plasma membrane, or ApoBDs, which are generated during programmed cell death, exosomes originate from endosomal compartments, forming intraluminal vesicles (ILVs) that are later released into the extracellular environment when multivesicular bodies (MVBs) fuse with the plasma membrane [17]. Additionally, exosomes are enriched with specific markers, including tetraspanins (CD9, CD63, CD81), ALIX, and TSG101, which distinguish them from MVs and ApoBDs that contain different surface markers and structural components [18].

Due to the essential function of intercellular communication in neurodegeneration, exosomes have become significant contributors to disease assessment and prospective treatment strategies [19]. Their ability to encapsulate and transport bioactive compounds, traverse the BBB, and influence cellular responses underscores their potential as biomarkers and therapeutic vectors in NDDs [20–23]. Additionally, recent studies indicate that exosome-like vesicles originated from plant sources possess structural similarities to mammalian exosomes and may facilitate neuroprotection by delivering bioactive compounds with antioxidant and anti-inflammatory properties [24, 25]. These plant-derived

vesicles are reported as highly biocompatible, stable, and easily scalable, making them promising candidates for future therapeutic use in NDDs [26].

This review assesses the newly recognized function of exosomes in NDDs, emphasizing their potential as biomarkers and therapeutic agents, especially for early diagnosis, disease monitoring, and targeted medication administration. Their function in intercellular communication concerning neurodegeneration is examined, highlighting their distinctive capacity to cross the blood–brain barrier, rendering them particularly advantageous for therapeutic uses. Additionally, the constraints related to their clinical application are examined, and prospective research avenues that may advance the creation of exosome-based treatments for NDDs are emphasized.

Overview of Major Neurodegenerative Diseases

AD represents the leading cause of dementia among elderly individuals, manifesting as progressive cognitive decline, memory impairment, and alterations in behavior [27]. Pathologically, AD is characterized by two defining features: extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein [28]. These aberrant protein aggregates interfere with synaptic communication, trigger neuroinflammatory responses, and ultimately result in extensive neuronal loss [29], particularly in the hippocampus and cerebral cortex—regions critically involved in memory and cognitive function [30]. The etiology of AD is multifactorial, encompassing genetic, environmental, and lifestyle influences [31]. Early-onset AD is strongly associated with mutations in the APP, PSEN1, and PSEN2 genes [32], whereas the APOE-ε4 allele is a major genetic risk factor for late-onset AD [33]. Other pathogenic contributors include oxidative stress, mitochondrial dysfunction, and chronic neuroinflammation [34]. Diagnosis of AD is based on a combination of clinical evaluation, neuroimaging, and the use of specific biomarkers, with a higher prevalence observed in women compared to men [35]. While current treatments, such as cholinesterase inhibitors and NMDA receptor antagonists, provide symptomatic relief, they do not halt disease progression [36]. Emerging therapies targeting amyloid-beta and tau proteins offer potential disease-modifying effects, yet their efficacy remains under investigation [37].

PD is a neurodegenerative disorder characterized by motor impairment due to the progressive loss of dopaminergic neurons in the substantia nigra [38]. Environmental factors, such as pesticide exposure, and genetic mutations in SNCA and LRRK2 are linked to disease development [39]. Dopamine depletion disrupts basal ganglia function, leading to the hallmark motor symptoms of PD [40]. The accumulation of Lewy bodies, primarily composed of misfolded α-synuclein, is the pathological hallmark [41]. Diagnosis is based on clinical motor assessments, supported by neuroimaging to exclude other conditions [42]. Treatment focuses on symptomatic relief with levodopa, dopamine agonists, and MAO-B inhibitors, while deep brain stimulation is used in advanced cases [43]. Key risk factors include age, family history, and exposure to neurotoxins, with an estimated ten million individuals affected globally, particularly those over 60 [39].

HD is a neurodegenerative disorder caused by a CAG repeat expansion in the HTT gene on chromosome 4, leading to the production of mutant huntingtin protein [44]. This aberrant protein aggregates in neurons, particularly within the cerebral cortex and basal ganglia, triggering progressive neurodegeneration and selective neuronal loss [45]. Clinically, HD presents with motor dysfunction and cognitive decline [46], and diagnosis is confirmed through genetic testing for the HTT mutation [47]. Neuroimaging techniques such as MRI often reveal cortical and basal ganglia atrophy [48]. Currently, there is no cure for HD [49], and management focuses on symptomatic relief, particularly for movement disorders and psychiatric symptoms, using agents such as tetrabenazine and antipsychotics [50]. Given its autosomal dominant inheritance pattern, individuals with an affected parent have a 50% risk of inheriting the mutation [51].

FTLD encompasses a group of neurodegenerative diseases characterized by progressive atrophy of the frontal and temporal lobes of the brain [52]. Symptoms vary based on the affected brain regions and may include personality changes, social withdrawal, speech difficulties, and impaired judgment [53]. Pathogenesis involves the accumulation of pathogenic proteins such as tau, TDP-43, and FUS, which lead to neuronal death and gliosis [54]. Familial cases are linked to mutations in genes like MAPT, GRN, and C9orf72, which promote abnormal protein aggregation [55]. Diagnosis is based on clinical assessment of behavioral and cognitive symptoms, supported by neuroimaging techniques like MRI and PET to observe brain atrophy patterns [56]. Genetic testing may be conducted in familial cases to identify specific mutations [57]. Currently, no cure exists, and treatment focuses on symptom management, with antidepressants and antipsychotics used to address mood and behavioral disturbances [58]. Supportive care, including speech and occupational therapy, plays a key role in enhancing quality of life for patients and their families. Risk factors for FTLD include advancing age and family history, with a higher incidence observed among individuals with affected first-degree relatives [59]. The prevalence is estimated at 15 to 22 cases per 100,000 people [60], primarily affecting individuals between 40 and 65 years of age [61]. Early diagnosis

and intervention can significantly improve patient outcomes and care planning [62].

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that primarily affects motor neurons in the brain and spinal cord, leading to muscle weakness, paralysis, and ultimately death [63]. Motor neurons control voluntary muscles involved in activities such as breathing, walking, and speaking [64]. As these neurons degenerate, muscle control deteriorates, while cognitive function is typically preserved, leaving patients fully aware of their condition [64]. Most ALS cases are sporadic with no clear genetic cause, while 5–10% are familial, often linked to mutations in genes such as SOD1, C9orf72, and TARDBP, which are associated with oxidative stress and protein misfolding [65]. Although no definitive environmental cause has been identified, factors like smoking, exposure to pollutants, and heavy metals may play a role in ALS development [66]. Patients often present with neuronal inclusions containing misfolded proteins such as TDP-43 [66]. Currently, there is no cure for ALS, and treatment focuses on symptom management [67]. Riluzole has shown efficacy in delaying disease progression by reducing glutamate toxicity, while edaravone may provide antioxidant benefits [68]. Multidisciplinary care, including respiratory support and physical therapy, is essential for improving quality of life [69]. Risk factors for ALS include male sex, advancing age (40–70 years), and family history, with occupational exposures [66] and military service also implicated [70]. ALS is considered a rare disease, affecting approximately 1–2 in every 100,000 people annually worldwide, with higher prevalence in North America and Europe [71]. Most patients survive 3–5 years post-diagnosis, although 10% live beyond 10 years [72].

SCA are a group of inherited neurodegenerative disorders characterized by progressive degeneration of the cerebellum, brainstem, and spinal cord, leading to ataxia—loss of coordination and balance [73]. SCAs are autosomal dominant, meaning a single mutated gene copy is sufficient to cause disease [74]. Over 40 subtypes have been identified, each linked to specific gene mutations, commonly involving CAG trinucleotide repeat expansions in genes such as SCA1, SCA2, SCA3 (Machado-Joseph disease), and SCA6 [75]. These mutations result in the formation of toxic protein aggregates, which cause neuronal death, particularly in the cerebellum [73]. Clinically, SCAs typically manifest in adulthood with symptoms including clumsiness, dysarthria, and ataxic gait, progressing to tremors, ocular movement difficulties, and fine motor impairments. Diagnosis is based on clinical assessment, MRI to detect cerebellar atrophy, and genetic testing to identify specific subtypes [76]. While no cure exists, management focuses on symptomatic relief, including physiotherapy to preserve mobility and medications for tremors and stiffness [73]. Risk factors include a family history of the disease, as SCAs are inherited [77]. The severity and onset can vary within families, often influenced by the length of the CAG repeat expansions. SCAs are rare, affecting 1–5 per 100,000 individuals globally, and the prognosis varies significantly depending on the subtype, with the progressive nature of the disease imposing a substantial burden on patients and healthcare systems [78].

MS is a chronic autoimmune disorder in which the immune system attacks the central nervous system, particularly affecting the brain, spinal cord, and optic nerves [79]. The immune-mediated destruction of the myelin sheath surrounding nerve fibers disrupts the transmission of nerve signals, leading to a range of neurological symptoms [80]. The damage results in scar tissue formation, or sclerosis, giving the disease its name. The cause of MS remains unclear, but it is thought to arise from a combination of genetic and environmental factors, including smoking, low vitamin D levels, and viral infections like Epstein–Barr virus [81]. MS is more common in regions farther from the equator and affects women two to three times more frequently than men [82]. Pathologically, MS is characterized by demyelination, axonal loss, and inflammation, resulting in lesions primarily in the spinal cord, optic nerves, and brain white matter [83]. Over time, neurodegeneration leads to irreversible disability [84]. MRI scans are essential for detecting areas of demyelination, and clinical evaluation and laboratory tests further assist in diagnosis [85]. MS management focuses on controlling symptoms, modifying disease progression, and enhancing quality of life [86]. Treatments include immunomodulatory drugs, such as interferon-beta, glatiramer acetate, and newer oral medications like fingolimod, as well as monoclonal antibodies like natalizumab and ocrelizumab. Progressive forms of MS remain challenging to treat, though ocrelizumab has shown promise in slowing disease progression [87]. Supportive care, including physiotherapy and medications for fatigue, pain, and spasticity, is crucial for symptom management [88]. Globally, MS affects over 2.8 million individuals, with an incidence of 100–150 cases per 100,000 people, typically presenting between the ages of 20 and 40 [89].

As seen across various neurodegenerative diseases, despite their distinct clinical manifestations, they share common pathological mechanisms, including protein aggregation, mitochondrial dysfunction, oxidative stress, neuroinflammation, and impaired cellular clearance pathways. These interrelated processes lead to neuronal loss and disease advancement, ultimately resulting in irreversible functional deterioration.
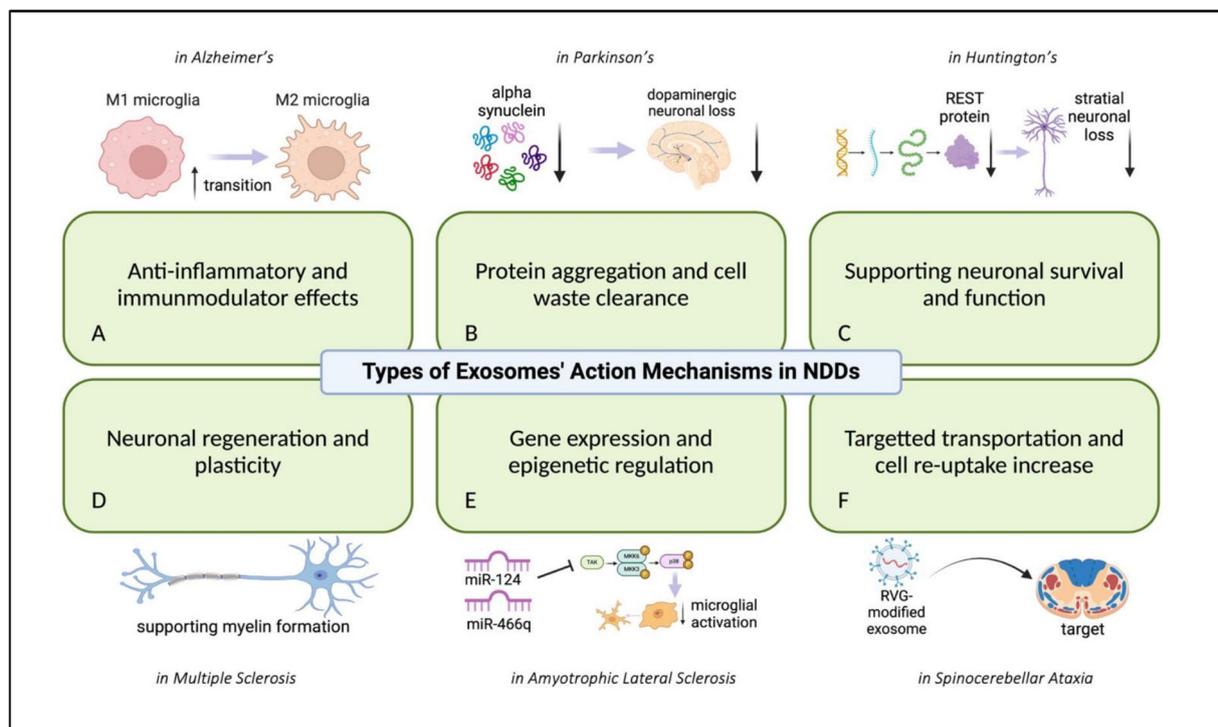
Exosomes in Neurodegenerative Diseases

As research on NDDs progresses, increasing attention has been given to the role of exosomes in disease monitoring and treatment. Given their ability to transport biomolecules,

traverse the blood–brain barrier, and indicate disease pathology, exosomes have become interesting candidates for biomarker identification and therapeutic applications in NDDs. Structurally, exosomes carry a diverse molecular cargo including proteins, lipids, RNA, and DNA, which they transport between cells, influencing a wide range of biological functions [90]. Due to their role in facilitating biomolecular transport, exosomes are essential in maintaining cellular homeostasis, as well as in regulating immune responses and inflammatory processes [91]. In recent years, exosomes have garnered significant interest in the field of neurodegenerative diseases (NDDs), such as Parkinson's disease, Alzheimer's disease, and Huntington's disease, as both potential biomarkers and therapeutic agents [92]. Their ability to reflect the molecular changes occurring within diseased cells positions exosomes as promising non-invasive diagnostic tools [93]. By transporting disease-specific molecules such as proteins, RNAs, and lipids, exosomes can provide early insights into disease onset and progression, offering new avenues for monitoring neurodegenerative conditions [94]. Moreover, exosomes possess unique therapeutic potential, particularly in neurodegenerative diseases. Their natural ability to cross the blood–brain barrier makes them ideal candidates for delivering therapeutic agents, including

drugs, RNA molecules, and gene-editing tools, directly to affected neurons [95]. This capability is crucial in developing targeted therapies aimed at modifying disease processes at the cellular level. Exosome-based treatments have the potential to modulate inflammation, reduce pathological protein accumulation, and restore cellular functions, thereby offering novel strategies for slowing or halting disease progression [96]. Exosomes exert their therapeutic effects in NDDs through multiple mechanisms, as illustrated in Fig. 1. In summary, exosomes represent a frontier in both the diagnosis and treatment of neurodegenerative diseases. Their distinctive ability to reflect cellular states and deliver targeted therapies underscores their potential in addressing the complex challenges posed by neurodegenerative conditions.

Current Applications of Exosomes as Biomarkers in Neurodegenerative Diseases

Exosomes are small extracellular vesicles released by cells and are recognized as significant indicators in neurodegenerative disorders [97]. Exosomes, due to their capacity to encapsulate and transport specific proteins, lipids,

Fig. 1 Types of exosomes' action mechanisms in neurodegenerative diseases (NDDs). Exosomes contribute to **A** anti-inflammatory and immunomodulatory effects, **B** protein aggregation and cell waste clearance, **C** neuronal survival and function support, **D** neuronal regeneration and plasticity, **E** gene expression and epigenetic regu-lation, and **F** targeted transportation and enhanced cell re-uptake. Representative examples of these mechanisms are illustrated for Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis, and spinocerebellar ataxia

RNAs, and DNAs, function as primary mediators of cellular communication and present substantial potential in the diagnosis of conditions such as Alzheimer's and Parkinson's [98]. Therefore, exosomes have been used as biomarkers in NDDs and recently several meta-analysis have been reported with regards to these properties [99–101]. In particular, exosomes found in the bloodstream represent an attractive biomarker for NDDs, owing to their relative abundance and accessibility in blood samples of the patients [102]. In Parkinson's disease, blood exosomes contain α-synuclein, an essential biomarker for disease development [103]; in Alzheimer's patients, increased amounts of amyloid-beta and phosphorylated tau proteins are present in circulating exosomes [104]. These blood-derived exosomal indicators enhance accuracy in diagnosis and enable noninvasive tracking of disease progression, resulting in early detection [105].

Although blood and cerebrospinal fluid (CSF) remain the primary sources of exosomes in current diagnostic methods, other biological fluids, including saliva, urine, sweat, breath, and tears, have attracted attention as non-invasive and promising alternatives. Saliva is a readily obtainable fluid that facilitates the collection of exosomes carrying amyloid-beta and tau proteins, which serve as unique biomarkers for Alzheimer's, therefore contributing in early neurological diagnosis [106]. Urine is an effective medium for analyzing disease-specific peptides or proteins in urine exosomes, as it can potentially obtained non-invasively and in considerable amounts. Although urine is a distant site to the central nervous system, it provides an acceptable tool to evaluate systemic responses to neurodegenerative disorders [107].

While sweat enables continuous monitoring, particularly via wearable devices, it is a complicated sample type due to the low concentration of exosomes and the influence of ambient conditions, such as temperature, on exosome yields [108]. On the other hand, breath presents the opportunity for noninvasive, real-time biomarker analysis as a novel source of biological fluids; while primarily investigated for respiratory problems, research on breath exosomes may enhance neurodegeneration diagnosis with improved collecting methods [109]. Interestingly, tears are a highly interesting material for noninvasive biomarker studies, since tear exosomes from Alzheimer's patients have demonstrated the presence of Alzheimer's-specific biomarkers [110]. Each of these diverse fluid sources provides novel approaches to enhance exosome-based diagnostic techniques, ensuring minimal patient discomfort for the early diagnosis and monitoring of neurodegenerative disorders. Table 1 summarizes the most current sources, detection methods, and clinical applications of exosomal biomarkers in neurodegenerative diseases. On the other hand, Fig. 2 illustrates the many bodily fluids in which exosomes can be found as well as their enriched content.

Therapeutic Mechanisms of Exosomes in Neurodegenerative Diseases

Exosomes have been recognized for their potential as therapeutic carriers in neurodegenerative diseases due to their unique ability to transport bioactive compounds across cellular barriers and modulate various cellular processes [131, 132]. Their adaptability as therapeutic agents can be classified into two main categories: the inherent effects resulting from their natural molecular composition, and the targeted therapeutic cargo that can be incorporated into them [19]. Through these mechanisms, they not only offer direct neuroprotective and anti-inflammatory effects but also function as customizable delivery vehicles for targeted molecular treatments. Several research in the literature have demonstrated that exosome-based treatments had direct and significant effect on functional recovery such as behavioral, physical, and cognitive improvements in in vivo models and clinical trials [133–135]. Specific literature examples of therapeutic usage and consequences of exosome-based therapies are illustrated in Fig. 3 and Table 2.

Intrinsic Therapeutic Effects of Exosomes

Exosomes exhibit inherent therapeutic potential due to their unique chemical composition and the bioactive compounds they intrinsically generate from their progenitor cells. This naturally occurring composition consists of lipids, surface proteins, and endogenous RNAs, all of which work together to make it possible for exosomes to participate in the control of cell signaling and the regulation of immunological function within the nervous system. In the context of neurodegenerative diseases, where chronic inflammation, oxidative stress, and disrupted signaling contribute to the progressive loss of neuronal function, these intrinsic effects are particularly beneficial. For example, Circ-Epc1, a circular RNA that affects microglial polarization, is naturally present in exosomes generated from adipose-derived stem cells (ASCs) [136]. In neurodegenerative conditions such as Alzheimer's disease, where neuroinflammation intensifies neuronal injury, Circ-Epc1 has been demonstrated to facilitate a transition from the pro-inflammatory M1 microglial phenotype to the anti-inflammatory M2 phenotype. This transition results in a decrease in the production of pro-inflammatory cytokines and a decrease in apoptosis within hippocampal neurons, thereby promoting neuroprotection and possibly reducing the progression of the disease. Furthermore, exosomes from macrophages have been shown to have an inherent capacity to improve the clearance of amyloid-beta (Aβ) in

Table 1 Exosomal biomarkers used in NDDs: source, detection methods, and clinical applications

Source	Types of NDDs	Exosomal biomarkers	Diagnostic tool	Clinical utility	Reference
Blood	Huntington's disease	Full-length Huntingtin protein (HTT) (360 kDa), mutant Huntingtin fragment (~70 kDa)	Ultracentrifugation, western blotting method	Potential biomarker for diagnosis and monitoring of therapy efficacy	[111]
Blood	Frontotemporal lobar degeneration and GRN/C9orf72 mutation	Cathepsin D levels (ng/sEV)	ELISA, nanoparticle tracking analysis (NTA)	Diagnostic potential with high performance (AUC = 0.85); correlated with age of onset and progressive disease states	[112]
Blood	Alzheimer's disease	Elevated levels of amyloid-β (1–42), phosphorylated Tau (p-Tau), synaptophysin, TNF-α, IL-1β, and GFAP	Chemical precipitation, transmission electron microscopy, nanoparticle tracking analysis, western blot, ELISA	Potential biomarkers for diagnosis, progression, and neuroinflammation	[113]
Blood	Amyotrophic lateral sclerosis	hsa-miR-34a-3p and hsa-miR-1306-3p for ALS patients with SOD1/C9orf72 mutations; hsa-miR-199a-3p and hsa-miR-30b-5p for patients with sALS	miRNA isolation, RT-qPCR	Potential biomarkers to distinct amyotrophic lateral sclerosis with mutant genes	[114]
Blood	Multiple sclerosis	CX3CR1$^+$/UCHL1$^+$, NMDAR2A$^+$, and NFL$^+$ microglial EVs	Nano flow cytometry	Potential biomarkers for diagnosing multiple sclerosis, distinguishing it from HTLV-1-associated myelopathy, and tracking disease duration	[115]
Blood	Dementia, Parkinson's disease, multiple sclerosis	21 candidate protein biomarkers including APOE, CDH1, CDH13, CELSR2, CHI3L1, CHL1, CLEC3B, CLU, CST3, FGA, FGB, FGG, FLNA, H2AC20, MAN2A1, OLFM1, RAB7A, SLC2A3, TMEM198, TNC, and TREML1	Magnetic transferrin nanoparticles (MTNs) assay for specific exosome isolation, high-throughput proteomics	Promising diagnostic biomarkers for minimally invasive diagnosis of dementia, PD, and MS	[116]
Blood	Alzheimer's disease	hsamiR-30b-5p, hsa-miR-22-3p, and hsa-miR-378a-3p	Western blot, RNA isolation, sequencing, qRT-PCR	Potential biomarkers for Alzheimer's disease and candidate for developing miRNA panel	[117]
Blood	Frontotemporal dementia and Alzheimer disease	Ng, MFN-2, LAMP-2, golgin A4	Single molecule array (Simoa) technique, SDS-PAGE, immunoblotting	Identifying common mechanisms and differences among neurodegenerative diseases	[118]
Blood	Alzheimer's disease	Aβ42, P-tau, and T-tau, GAP43, SNAP25	ELISA	identification of effective biomarkers for prediction of AD 5 to 7 years before cognitive impairment	[119]
Blood	Alzheimer's disease	APOC3, APOH, C4BPα, CO3, KV230, AACT isoform 1, CO9, IGHM isoform 2, K2C6A	Precipitation-based isolation, column-based-isolation, mass spectrometry	Potential candidates for biomarker of Alzheimer disease and representation of disease progression	[120]
Cerebrospinal fluid, blood	Spinal muscular atrophy	Full-length SMN (flSMN) transcript	Droplet digital PCR, ultra-sensitive single molecule array	Potential biomarker and monitoring treatment response	[121]

Table 1 (continued)

Source	Types of NDDs	Exosomal biomarkers	Diagnostic tool	Clinical utility	Reference
Cerebrospinal fluid	Amyotrophic lateral sclerosis	Exosomal mRNAs with significant differential expression, including CUEDC2, TUBB3, and CAMK2A	Next-generation sequencing (NGS), DESeq2 for differential expression	Candidate biomarkers for ALS with potential in diagnosis and tracking disease mechanisms	[122]
Cerebrospinal fluid	Amyotrophic lateral sclerosis	increased levels of novel INHAT repressor (NIR); decreased levels of 11 unspecified proteins	Gel filtration chromatography, liquid chromatography-tandem mass spectrometry	Potential biomarker for ALS diagnosis and monitoring; indicates nucleolar stress involvement in ALS pathogenesis	[123]
Cerebrospinal fluid	Alzheimer's disease, Parkinson's disease, dementia, and their subtypes	37 disease-specific protein biomarkers identified	Label-free mass spectrometry	Potential biomarkers for differential diagnosis of dementia types and tracking of neurodegenerative progression	[124]
Cerebrospinal fluid	Huntington's disease	Mutant Huntingtin protein (mHTT) levels in CSF as a pharmacodynamic biomarker	Antisense oligonucleotide therapy, viral expression techniques	Potential biomarker for monitoring mHTT reduction in the striatum; useful for evaluating therapeutic target engagement in the CNS for HD	[125]
Saliva	Alzheimer's disease, cognitive impairment	Elevated levels of oligomeric amyloid-beta (Aβ), phosphorylated tau protein (p-tau), and CD63	Nanoparticle tracking analysis (NTA), automated western blot analyzer, fluorescent antibody quantification	Non-invasive, cost-effective screening method for AD and cognitive impairment progression	[126]
Saliva	Alzheimer's disease	miRNA-485-3p associated with Aβ deposition	qRT-PCR, ROC curve analysis	Non-invasive biomarker for predicting Aβ-PET positivity; high diagnostic accuracy for Alzheimer's disease	[106]
Urinary	Alzheimer's disease	Aβ1–42 and P-S396-tau	Transmission electron microscopy; nanoparticle tracking analysis, ELISA	Potential biomarkers detection for early diagnosis of Alzheimer's disease	[127]
Urinary	Alzheimer's disease	miR-196b-5p, miR-339-3p, miR-34a-5p, miR-376b-3p, miR-677-5p, and miR-721	MicroRNA microarray, droplet digital polymerase chain reaction	Exploring differences in initial Aβ-plaque deposition and potential noninvasive biomarkers	[128]
Urinary	Alzheimer's disease	Annexin 2 and Clusterin	BCA assay, liquid chromatography tandem mass spectrometry, nanoparticle tracking analysis, transmission electron microscopy, western blot, ELISA	Potential non-invasive source of biomarkers for potentially early intervention of Alzheimer's disease	[129]
Tears and cerebrospinal fluid	Multiple sclerosis	TGFB1, ANGPT2, VEGFA proteins; beta-estradiol, progesterone hormones	Flow cytometry, FASP digestion, dynamic laser light scattering, liquid chromatography tandem mass spectrometry	Unveiling of cross talk between CSF and tears; new diagnostic perspectives for multiple sclerosis	[130]
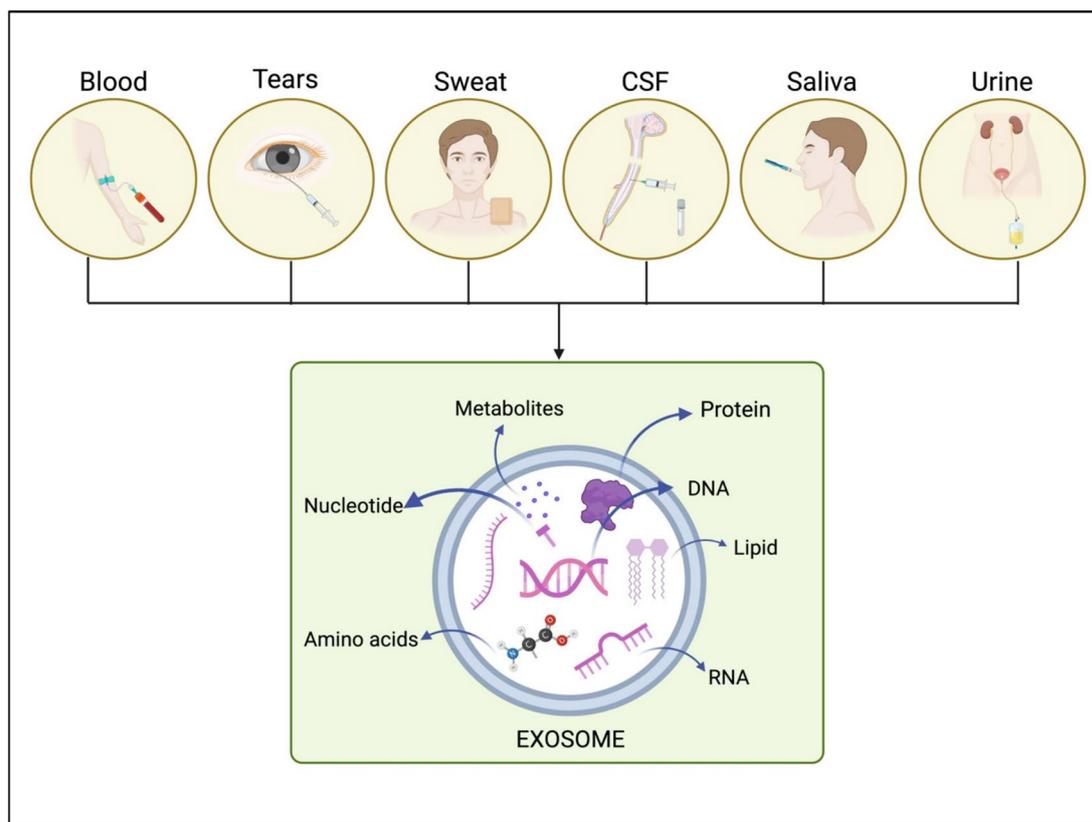
Fig. 2 Depiction of exosome composition and its origins from bodily fluids. Exosomes transport many biomolecules, such as RNA, DNA, proteins, lipids, nucleotides, amino acids, and metabolites that enable intercellular communication. Common biological fluids, including blood, cerebrospinal fluid, saliva, perspiration, tears, and urine, provide accessible sources for exosome isolation and biomarker identification

Alzheimer's models [137]. They promote Aβ uptake and lysosomal damage through natural interaction with microglia, thereby reducing the harmful accumulation of amyloid plaques, a characteristic of Alzheimer's pathogenesis. This natural clearance mechanism emphasizes the inherent anti-amyloidogenic characteristics of exosomes and highlights their potential as therapeutic agents for treating critical clinical aspects of neurodegenerative disorders. Besides their impact on neuroinflammation and amyloid-beta clearance, they intrinsically facilitate cell-to-cell communication, enabling the modulation of neuronal survival pathways [138]. Their lipid bilayer composition and related proteins enable interactions with cellular receptors in target cells, triggering signaling cascades that enhance cellular resilience to oxidative stress and other neurotoxic threats. These intrinsic functions render exosomes both adaptable and inherently suited to the treatment requirements of neurodegenerative disorders. The range of intrinsic therapeutic effects documented in recent research is summarized in Table 2.

Therapeutic Impact of Exosome Cargo Molecules

Exosomes can transport and deliver unique therapeutic cargo molecules that can be externally loaded to target specific disease pathways, greatly increasing their therapeutic potential [139, 140]. The cargo molecules comprise various RNA types (including microRNAs and messenger RNAs), proteins, and small molecules that can be selected for their ability to modulate disease-related processes, such as apoptosis, inflammation, and protein aggregation [141]. By means of specific loading of these compounds, exosomes function as precise delivery systems that enhance their therapeutic potential beyond their inherent characteristics [142].

For instance, miR-124 is loaded into exosomes and used in models of Huntington's disease [143]. miR-124 has the ability to downregulate RE1-silencing transcription (REST) mRNA, a regulator linked to Huntington disease. By diminishing REST levels, exosomes containing miR-124 alleviate detrimental gene expression alterations linked to the disease, providing a gene-targeted strategy that addresses the
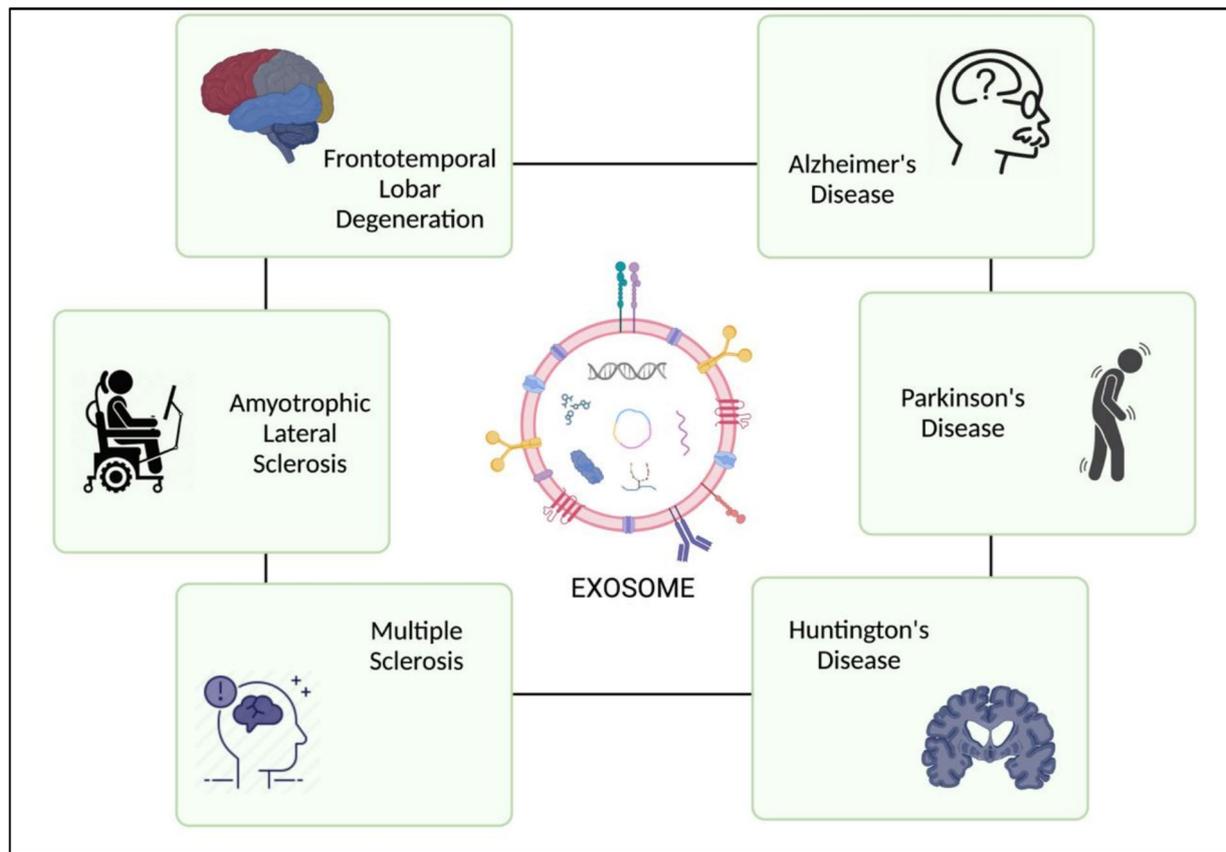
Fig. 3 Schematic depiction of exosomes and their role in prominent neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD), and multiple sclerosis (MS). Exosomes are essential for intercellular communication as they transport macromolecules, including proteins, RNA, and lipids, positioning them as possible diagnostic indicators and therapeutic instruments in certain circumstances

fundamental causes of neuronal toxicity in Huntington's. On the other hand, exosomes loaded with anti-inflammatory agents exhibit considerable therapeutic advantages, especially in neuroinflammatory conditions such as multiple sclerosis. Macrophage-derived exosomes containing resveratrol suppress the NF-κB signaling pathway in multiple sclerosis models, resulting in decreased inflammatory cytokine production and mitigated demyelination in the central nervous system [144]. The attenuation of neuroinflammation is essential for decelerating the advancement of MS, wherein immune cell infiltration and inflammation significantly influence disease severity. In addition to RNA and small molecule delivery, exosomes can be modified to transport neurotrophic substances that promote neuronal survival and repair processes. For instance, exosomes containing brain-derived neurotrophic factor (BDNF) generated from human umbilical cord mesenchymal stem cells (MSC) have demonstrated potential in models of Parkinson's disease [145]. BDNF facilitates neuronal regeneration, diminishes apoptosis, and safeguards neurons against ferroptosis, a form of cell death linked to iron accumulation and oxidative

stress. Exosomes stimulate the regeneration of dopaminergic neurons and improve motor function recovery in Parkinson's disease animals by delivering BDNF directly to the damaged regions. In conclusion, the versatility and targeted therapeutic capabilities of exosome cargo molecules—which encompass specific miRNAs, proteins, and other therapeutic agents—are critically dependent on their impact. These cargo molecules allow exosomes to have a highly specific impact on gene expression and cellular pathways within recipient cells, providing a precise method of addressing the mechanisms of neurodegenerative diseases. Tablo 2 provides a comprehensive overview of the therapeutic cargo molecules and their documented effects in recent studies.

Future Trends and Potential of Exosomes as Therapeutic Agents

Exosomes present significant potential as therapeutic agents in neurodegenerative diseases, providing unique opportunities for drug delivery, overcoming biological barriers such

Table 2 Therapeutic effects and outcomes of exosomes in neurodegenerative diseases

Types of NDS	Exosome source	Therapeutic molecule	Mechanism of action	Therapeutic outcome	Reference
Parkinson's disease	Human umbilical cord mesenchymal stem cell	Brain-derived neurotrophic factor (BDNF)	Suppression of apoptosis and ferroptosis; promotion of neuronal cytoskeletal stability	Facilitates neuronal repair and regeneration by augmenting nigrostriatal pathway functionality and has neuroprotective impact	[145]
Parkinson's disease	Dendritic cells	Rabies virus glycoprotein (RVG)–modified exosomes laden with shRNA-minicircles	Downregulation of alpha-synuclein expression	Decrease in alpha-synuclein aggregations, reduction in loss of dopaminergic neurons in substantia nigra pars compacta	[146]
Parkinson's disease	Human umbilical cord mesenchymal stem cell	miR-133b	Decreases the phosphorylation level of Tau protein by targeting RhoA-ROCK signaling pathway	Improvement in motor function, reduced depression, enhanced dopaminergic neuronal function	[147]
Alzheimer's disease	Adipose-derived stem cell	Circ-Epc-1	Decrease in M1 microglial differentiation, promotion of M2 microglial differentiation	Decrease in inflammatory cytokine expressions and decrease of apoptosis in hippocampal neurons, improving cognitive function by neuronal damage decrease	[136]
Alzheimer's disease	Macrophage	Mannose-modified exosomes laden with gemfibrozil	Decrease in amyloid fibril formation, promotion of Aβ intake by microglia, acceleration of lysosome-mediated Aβ clearance	Mitigation of cognitive impairment and alleviation of neuronal damage	[148]
Alzheimer's disease	Rat-bone marrow mesenchymal stem cells and human embryonic kidney 293 cells	miR-29b	Downregulation of BACE1, enhancement of PKA/CREB signaling inhibition of neuronal apoptosis	Improvement in spatial learning and memory, reduction of Aβ-induced cognitive deficits	[149]
Multiple sclerosis	Mesenchymal stem cell	LJM-3064 aptamer	Immunomodulation	Reduction in demyelination region—brain damage—and inflammatory cell infiltration into central nervous system	[150]
Multiple sclerosis	Macrophage	Resveratrol	Inhibition of NF-κB pathway	Decrease in inflammatory responses, inflammatory cell infiltration in central nervous system, demyelination	[144]
Huntington's disease	Human embryonic kidney cells	miR-124	Binding to RE1-silencing transcription (REST) mRNA	Reduction in REST expressions in striatum; no production of significant behavioral improvement	[143]
Huntington's disease	Neural stem cells	DNAJB6	DNAJB6 binds to misfolded polyglutamine (polyQ) and facilitates their transfer to other chaperones	Decrease in polyQ aggregation in striatum	[151]
Spinocerebellar ataxias	Human olfactory ensheathing cells	has-miR-6780	Inhibition of PI3KR5-related autophagy inhibition	Decrease in expression of polyQ, increase in expression of LC3II/I and improved motor coordination, getting benefit from butylidenephthalide	[152]
Spinocerebellar ataxias	HEK293 cells	miR-25 and miR-181a in RVG-modified exosomes	Inhibition of mutATXN3 expression	Decrease in mutATXN3 mRNA and improvement in motor ability and balance	[153]

Types of NDS	Exosome source	Therapeutic molecule	Mechanism of action	Therapeutic outcome	Reference
Table 2 (continued)					
Amyotrophic lateral sclerosis	Mesenchymal stem cells	miR-467 and miR-466q	Reduction in the activation of the p38 MAPK pathway	Beneficial anti-inflammatory effect on pro-inflammatory microglia	[154]

as the blood–brain barrier (BBB), and contributing to clinical applications. This section discusses emerging trends and prospective breakthroughs.

Exosomes as Targeted Drug Delivery Vehicles

Exosomes exhibit inherent characteristics like biocompatibility, stability, low toxicity, and reduced immunogenicity, rendering them optimal candidates for drug administration. These vesicles inherently transport various cargo, such as DNA, RNA, proteins, lipids, and metabolites, allowing them to influence biological processes in destination cells [155]. Moreover, exosomes can be modified to transport therapeutic agents with greater precision, hence augmenting their clinical efficacy [156, 157]. Recent developments have shown that therapeutic miRNAs, like miR-124 and miR-520f-3p, can be successfully loaded into exosomes to treat 6-hydroxydopamine (6-OHDA)-induced Huntington's disease in mice, improving neuronal survival and reducing cell death [158]. The surface of exosomes is enriched with proteins, including transmembrane proteins, integrins, CD63, CD9, and CD81, which can function as both biomarkers and targeting ligands [159]. In addition to natural targeting, scientists have effectively modified exosomal surfaces chemically, physically, and genetically [160]. The lipid bilayer can be coupled with peptides, ligands, antibodies, chimeric antigen receptors (CARs), and DNA/RNA aptamers to improve the functionality and selectivity of exosomes [161]. For instance, in an in vivo model of Alzheimer's disease, exosomes containing RVG peptides and a genetically engineered CD10 variant demonstrated enhanced efficacy in targeting amyloid-beta aggregates and improved hippocampal delivery. Additionally, the CD10 variation increased the production of anti-inflammatory cytokines, providing a potentially effective therapy strategy for Alzheimer's disease [162]. On the other hand, utilizing cutting-edge imaging methods as photoacoustic imaging, fluorescence imaging, bioluminescence imaging, radionuclide imaging, CT scans, and magnetic resonance imaging allows for the targeted delivery and in vivo monitoring of exosomes [163]. For example, scientists created an imaging mouse model to detect the long-term accumulation of exosomes in vivo using bioluminescence resonance energy transfer (BRET) technology. Cancer cells expressing CD63-Antares2, which emits luminescence, were implanted into mice to provide a xenograft animal model in which cancer-targeting medications can be investigated as an exosome imaging tool [164]. In another study, researchers created a sensor utilizing fluorescence resonance energy transfer (FRET) technology to track conformational changes. They focused on exosomal EGFRs, and their sensor "ExoSen (exosome sensor)" facilitated the quantification of exosomal EGFRs in both in vivo and in vitro cellular investigations [165]. In another study,

researchers employed 64Cu and 68 Ga with fluorescence dyes to observe exosome distribution in vivo and ex vivo utilizing PET and optical imaging [166]. These technologies provide precise tracking of exosome biodistribution, facilitating the enhancement of their therapeutic uses.

Exosomes as Key Players in Crossing the Blood–Brain Barrier

The BBB is a selective barrier comprised of various cell types, including endothelial cells, pericytes, astrocytes, and microglia. This barrier comprises tight junctions (TJs) and adherens junctions (AJs) between cells, safeguarding the central nervous system (CNS) from macromolecules (e.g., polypeptides, nucleic acids, and proteins), while over 98% of small molecules and immune cells originate from blood circulation [167, 168]. Despite neurological diseases being the second leading cause of death globally, the systemic administration of diagnostic and therapeutic agents has been impeded in achieving efficacy due to the presence of the BBB [169].

Exosomes penetrate cells via paracellular and transcellular routes while passing through the BBB. In paracellular routes, passive diffusion serves as the primary mechanism for exosome translocation. Since this form of crossing is actualized in TJs and many exosomes are higher than these openings, further research is needed; nonetheless production of inflammatory cytokines and certain physiological situations can cause this situation [170]. Normal exosomal transport into brain tissues occurs via direct fusion, macropinocytosis, clathrin-mediated endocytosis, caveolin-mediated endocytosis, and phagocytosis [171]. For instance, in a co-culture setup that resembled the blood–brain barrier, ginseng-derived exosomes demonstrated effective penetration across closely spaced epithelial cells, such as C6 glioma cells and brain capillary endothelial cells (BCECs). The research indicated that ginseng-derived exosome-like nanoparticles (GENs) may serve as prospective agents to impede glioma progression and regulate tumor-associated macrophages (TAMs), demonstrating anti-tumor immune responses and inhibition of tumor progression [172]. After entrance of exosomes into cells, they are guided to endosomes or lysosomal destruction and lysosomal degradation of exosomes regulates downstream processes [173].

Furthermore, it has been demonstrated that the integrity of the blood–brain barrier and the physiological condition of the brain are related to exosomal blood–brain penetration [174]. In a study, serum-derived exosomes from healthy rats were given to a brain microvascular endothelial cell type (bEnd.3) that was lacking oxygen and glucose and to rats that had a middle cerebral artery occlusion (MCAO). Serum exosomes were discovered to inhibit LC3B-mediated autophagy and reduce apoptosis in cerebral ischemic/reperfusion rat striatum by boosting the Bcl-2/Bax ratio and decreasing the expression of cleaved caspase-3 in the cortex. By preventing endothelial cell death and autophagy-mediated tight junction protein degradation, this study demonstrated that serum exosomes preserve the integrity of the blood–brain barrier [175]. In a separate study, researchers assessed quiet (Q-Neu) and activated neutrophil (A-Neu) exosomes in a transient middle cerebral artery occlusion-hemorrhagic transformation (tMCAO-HT) model, measuring permeability and trans-endothelial electrical resistance (TEER) to evaluate blood–brain barrier (BBB) integrity. The miRNA profiles of both neutrophils indicated that genes associated with the positive regulation of endothelial barrier formation, cell junctions, interactions between the extracellular matrix and receptors, and the VEGF pathway were targeting. Their findings indicated that Q-Neu exosomes do not significantly affect BBB integrity; nevertheless, the exosomal trafficking of miRNAs from A-Neu-derived exosomes may exacerbate BBB injury [176]. On the other hand, a recent study demonstrated that exosomes obtained from human induced pluripotent stem cell–derived neural stem cells (hiPSC–NSC–Exo) enhance blood–brain barrier function and reduce leukocyte infiltration after intracerebral hemorrhage. The intra-nasal administration of hiPSC–NSC–Exo led to a reduction in monocyte chemoattractant protein-1 production, mediated by the activation of the PI3K/AKT pathway in astrocytes [177]. Overall, the important ability of exosomes to traverse the blood–brain barrier and their essential functions in preserving their integrity will expand opportunities in the field of neurodegenerative disease research, accompanied by the emergence of novel methodologies and approaches.

Exosome-Based Therapies in Clinical and Pre-clinical Trials

The majority of exosome-based clinical research on neurodegenerative illnesses is conducted on stem cells because of their immunosuppressive and regenerative capabilities, which have shown promise in recent years [178]. According to a recently published study, miR-29 expression is considerably reduced in Alzheimer's disease (AD) patients, indicating that it plays in disease pathogenesis. To investigate therapeutic possibilities, researchers introduced miR-29 into target cells and collected exosomes produced by those cells. Rat bone marrow mesenchymal stem cells and HEK-293 T cells were transfected with recombinant expression vectors that carried miR-29a or miR-29b precursor sequences. The modified exosomes were examined for their capacity to ameliorate the pathogenic consequences of amyloid-β (Aβ) peptide in a rat model of Alzheimer's disease. It was revealed that injecting miR-29-containing exosomes into the CA1 region of the rat brain reduced Aβ-related memory

and spatial learning impairments [149]. In another study, exosomes generated from mesenchymal stem cells (MSC-exosomes) were co-cultured with human neural cells from familial Alzheimer's disease and subsequently injected into transgenic mice. Behavioral assessments performed on these mice demonstrated notable enhancements in memory, cognitive abilities, and cerebral glucose metabolism. In cell culture assays, MSC-derived exosomes decreased Aβ expression and restored genes associated with memory and plasticity. It was determined that MSC-exosomes provide a promising cell-free therapeutic alternative for the treatment of Alzheimer's disease [179]. Another recent study investigated the potential therapeutic benefits of adipose-derived stem cell extracellular vesicles (ASC-EVs) for patients with spinal muscular atrophy (SMA). SMNΔ7 animals, a severe SMA type II model, were given intracerebroventricular injections of isolated murine ASC-EVs during the neonatal phase. When compared to controls, the treatment group had better motor function and less apoptotic activation, according to behavioral tests and histological investigations. ASC-EVs were found to effectively replicate the neuroprotective effects of their progenitor mesenchymal stem cells, making them potential candidates for SMA therapy, either alone or in combination with drugs [180]. In another study, human adipose–derived stem cell–derived exosomes (ADSC-exo) were investigated as therapeutic agents in the realm of amyotrophic lateral sclerosis. ADSC-exo was administered to primary neuronal stem cells isolated from wild-type and G93A ALS mice during neuronal differentiation by researchers. The treated cells exhibited a substantial decrease in mutant SOD1 aggregation in the cytoplasm compared to the untreated ALS control cells by the tenth day of differentiation. Furthermore, the phospho-CREB/CREB ratio and PGC-1α expression levels normalized as a result of ADSC-exo treatment, indicating that exosomes may be able to protect cells from the aberrant mitochondrial protein expression that is associated with ALS [181]. Similarly, another study found that exosomes from murin adipose–derived stromal cells can treat NSC-34 cells that are like motoneuron and were transfected temporarily or permanently with human mutant SOD1 genes (G93A, G37R, or A4V). Cells maintained under oxidative stress conditions induced by H_2O_2 showed markedly enhanced viability suggesting the protective effect against to oxidative damage, a critical factor in ALS pathogenesis, when treated with exosome therapy [182].

Apart from the pre-clinical studies, clinical trials utilizing exosomes in NDDs have also being conducted. In a study, researchers delivered mesenchymal stem cell–secreted exosomes (MSCs-Exos) intravenously to Alzheimer's disease (AD) patients, which previously eased the condition in mice models. This is the first clinical trial in patients, with dose selection prior to phase II and phase III clinical trials. Researchers carried out this study to evaluate the safety and efficacy of allogenic human adipose MSCs-Exos in individuals with mild to moderate Alzheimer's disease (AD). The amount of amyloid or tau that was deposited did not change significantly. However, the volume of the hippocampus shrunk in people who received a medium dose of exosomes. The study established a suitable dosage for the internasal administration of MSCs-Exos, which is safe and well-tolerated [183]. In another phase I clinical trial, researchers administered allogenic exosomes derived from human umbilical cord mesenchymal stem cells (HUC-MSCs) intrathecally to patients with subacute spinal cord damage (SCI) to assess safety and possible efficacy. Neurological assessments were conducted prior to the application, and the intrathecal delivery of allogeneic HUC-MSC exosomes was demonstrated to be safe. Furthermore, the study indicated possible clinical and functional enhancements in patients with subacute spinal cord injury [178].

In conclusion, exosome-based therapeutics have shown promise in clinical trials, and the recent studies are given in Table 3. However, additional research and advanced clinical studies (phase II/III) are required to confirm their efficacy and safety. This next generation therapeutics may serve as a great potential to successfully address the growing incidence of neurodegenerative illnesses.

Discussion

Exosomes have garnered significant attention as both biomarkers and therapeutic tools in the field of neurodegenerative diseases, offering unique, non-invasive approaches for diagnosis, monitoring, and treatment. Unlike traditional biomarkers, which can be invasive or costly, exosome-based strategies promise accessible and personalized insights into disease mechanisms [184, 185]. This review evaluated recent studies on exosome applications, highlighting their distinct properties and potential to reshape neurodegenerative disease research while underscoring the challenges that must be addressed for clinical translation.

One critical aspect across studies is the unique protein and nucleic acid cargo contained within exosomes isolated from neurodegenerative disease patients [186]. These exosomes, derived from various body fluids—including blood, cerebrospinal fluid, urine, saliva, sweat, and tears—carry disease-specific markers that reflect the pathological state of the brain, offering a valuable foundation for biomarker development [187]. Exosomal biomarkers, particularly those found in accessible fluids like blood, saliva, sweat, and tears, stand out as non-invasive, cost-effective, and rapid alternatives to traditional detection methods like brain imaging or cerebrospinal fluid punctures, which can be invasive, costly, and time-consuming [188]. Each body

Table 3 Clinical trials of exosomes used in neurodegenerative disease

Clinical trial ID or Pubmed ID	Dates	Type of disease	Therapeutic agent/ diagnostic bio-marker	Source of exosome	Status	Sponsor
NCT06598202	S: 2024.12.01 C: 2026.05.30	Amyotrophic lateral sclerosis	Exosomes derived from human umbilical cord blood mesenchymal stem cells	Human umbilical cord blood derived mesenchymal stem cells	Recruiting phase I/II	Xuanwu Hospital, Beijing
NCT04388982	S: 2020.07.01 C: 2022.08	Alzheimer's disease	Exosomes derived from allogenic adipose MSCs	Allogenic adipose MSCs	Unknown phase I/II	Ruijin Hospital
NCT06501469	S: 2022.03.23 C: 2030.03.25	Parkinson's disease	Not stated	Blood	Recruiting	Anonym
PMC7963893	2021	Alzheimer's disease	miR-193b	Serum	Completed	National Natural Science Foundation of China
PMC5888398	2018	Alzheimer's disease	Specialized synaptic proteins	Neurons	Completed	Michael J. Fox Foundation for Parkinson's Research, the Alzheimer's Association, Alzheimer's Research United Kingdom, and the Weston Brain Institute
PMC6459135	2019	Parkinson's disease	Brain insulin-signaling proteins	Neurons	Completed	University College London

fluid, however, presents unique logistical and technical considerations [189]. Blood offers a high yield but requires careful purification due to its rich protein content, while cerebrospinal fluid provides the most direct link to central nervous system activity but is invasive to collect. Saliva, sweat, and tears represent promising non-invasive options, with saliva offering easy and routine collection and wearable devices potentially enabling sweat sampling, though all may yield lower exosome concentrations [190]. For example, specific proteins associated with Alzheimer's disease have been detected in circulating exosomes from both blood and cerebrospinal fluid, demonstrating their potential as accessible tools for real-time disease monitoring [191]. Moreover, this disease-specific profiling offers promising avenues for early diagnosis and tracking disease progression, which is critical in neurodegenerative conditions. However, methodological variations—such as differing isolation techniques across body fluids and assay sensitivities—can impact biomarker accuracy and reliability [192]. Studies have shown that while some isolation methods maximize exosome yield from fluids like blood or cerebrospinal fluid, they may compromise purity, raising concerns about biomarker specificity [193]. To enhance reproducibility and clinical applicability, future research should prioritize standardizing protocols for exosome isolation and analysis across different body fluids [194].

On the other hand, despite attempts to enhance exosome extraction from diverse biofluids, considerable obstacles persist in standardizing methods to guarantee reproducibility and clinical relevance. For example, in a clinical trial, plasma BACE1-AS levels showed no significant difference between AD patients and the healthy group [195]. However, in a prior research, the situation was exactly the opposite, showing a great difference between healthy control group and AD patients [196]. Yield variation is a significant issue, as certain biofluids intrinsically yield lower exosome concentrations, requiring highly sensitive testing techniques. Furthermore, variations in protein content among biofluids can hinder isolation efficiency, necessitating additional purification processes for high-protein fluids such as blood to preserve biomarker specificity. Specifically, one issue arises from the complex origin of CSF and peripheral blood exosomes. In a clinical trial searching if miR-193b detection in exosomes is a potential diagnostic biomarker in AD, the variability in the source of exosomes can lead to ineffective isolation and detection of high-miR-193b exosomes, resulting in false negative results in patients [197]. Hence, future research must concentrate on creating standardized,

high-yield, and reproducible isolation methodologies for exosomes, specifically designed for each biofluid source, to maximize their utility as diagnostic tools.

Advancements supporting the use of exosomes as biomarkers are closely tied to the strengths and limitations of various detection technologies. Microfluidic platforms, which enable rapid and precise exosome isolation, are particularly advantageous due to their low cost and suitability for small sample volumes; however, the lack of full standardization may affect result consistency across studies [198]. Nanoparticle tracking analysis provides highly accurate measurements of exosome size and concentration, yet its high cost and specialized technical requirements limit broader use [199]. Fluorescence and optical microscopy techniques allow visualization of specific surface proteins, offering an advantage in multi-marker detection, though these methods may incur additional costs and time due to the need for specific staining [200]. Meanwhile, some highly sensitive technologies struggle to completely differentiate exosomes from other cellular particles, potentially impacting biomarker purity, which is critical for clinical diagnosis. Considering the heterogeneity of exosomes, advanced detection methods that distinguish exosome subtypes by cellular origin could enhance biomarker precision, particularly for neurodegenerative conditions where neural-derived exosomes hold significant diagnostic value [201]. Developing low-cost, high-precision, and portable solutions in exosome detection technologies will be essential for making exosomes more accessible in clinical diagnostic and monitoring settings [202]. Additionally, integrating these detection techniques with multi-omics approaches, such as proteomics and transcriptomics, could deepen our understanding of exosomal content and improve disease-specific profiling, potentially making lab-on-a-chip devices suitable for point-of-care diagnostics and routine disease monitoring across various body fluids [203]. Portable platforms, such as lab-on-a-chip devices, represent a promising future in exosome detection across various body fluids [204, 205].

In addition to their role as biomarkers, exosomes have shown considerable promise as delivery vehicles for therapeutic agents, particularly for their ability to cross the blood–brain barrier (BBB) with ease. This natural capacity distinguishes exosomes from other nanoparticle-based delivery systems, which often encounter significant challenges in penetrating the BBB and reaching target neural tissues [206]. Leveraging this advantage, recent studies have encapsulated therapeutic molecules, including siRNA, small-molecule drugs, and neuroprotective agents, within exosomes isolated from body fluids like blood and cerebrospinal fluid to deliver targeted treatments to neurodegenerative pathways [207]. Compared to conventional delivery approaches, exosomes offer a minimally invasive, biocompatible, and potentially cost-effective strategy for targeted therapy, making them

highly feasible for clinical practice [208]. Advances in exosome engineering have further expanded their versatility, enabling the delivery of complex therapeutic cargos such as CRISPR/Cas9 for gene editing or anti-inflammatory agents aimed at modulating neuroinflammation [209, 210]. Despite these promising developments, challenges remain regarding targeting specificity and off-target effects; ensuring that exosomes can selectively deliver therapeutic agents to diseased cells without affecting healthy tissue is critical [211–213]. Long-term biocompatibility and stability are also essential considerations, given the delicate nature of neural tissue and the need for consistent therapeutic efficacy [214, 215]. Addressing these issues through rigorous preclinical and clinical studies will be vital to advancing exosome-based delivery systems toward safe and effective use in treating neurodegenerative diseases.

Furthermore, differentiating exosome profiles from various neurodegenerative diseases, such as Alzheimer's, Parkinson's, and ALS, is essential for both diagnostic and therapeutic applications. Distinct exosome profiles have been observed in patients with each disease across different body fluids, offering a valuable method for differential diagnosis [216]. For example, variations in exosomal content between CSF and blood samples have been linked to specific pathologies, suggesting that fluid-specific markers could significantly enhance diagnostic accuracy [124]. This specificity underscores the potential of exosome-based diagnostics to provide more personalized, precise, and minimally invasive tools compared to traditional biomarkers. Differentiating between these diseases is crucial, as they often present with overlapping symptoms yet require distinct treatment approaches. However, while some studies demonstrate high sensitivity and specificity of exosomal biomarkers, variability in exosome content across patients, disease stages, and body fluids presents a challenge for achieving consistent diagnostic accuracy [217]. Addressing this heterogeneity will require technological advancements and standardized protocols, especially in cross-study comparisons. More comprehensive studies with larger sample sizes and diverse cohorts are needed to clarify these variations and strengthen the diagnostic validity of exosomes, ultimately advancing their application in personalized neurodegenerative disease management [218].

As exosome-based diagnostics and therapies advance rapidly towards clinical application, their complex nature and potential risks underscore the necessity for rigorous regulatory oversight in a largely undeveloped regulatory landscape, posing significant challenges. Exosomes are not classified as advanced therapy medicinal products (ATMPs) unless used for gene therapy, complicating their regulatory pathways in Europe and the USA [219]. This classification ambiguity impacts regulatory strategies and development plans, emphasizing the need for clear guidelines for their

use as biological medicinal products. The absence of standardized guidelines for exosome characterization, production reproducibility, and safety assessments further complicates the pathway toward clinical implementation [220]. Ethical considerations—particularly around patient consent and the long-term monitoring of exosome-derived treatments from body fluids—present additional challenges. The collection and analysis of body fluids must respect patient autonomy and privacy [221]. Moreover, long-term monitoring is necessary to assess the safety and efficacy of exosome-based treatments, raising ethical concerns about patient follow-up and data management [222]. Establishing robust regulatory frameworks that ensure safety, efficacy, and ethical standards will be critical in advancing exosome-based applications from research to practice. Achieving this requires a high level of cooperation among policymakers, researchers, clinicians, and regulatory authorities to develop comprehensive standards that address these regulatory and ethical concerns while fostering innovation in a manner that prioritizes patient safety and ethical integrity [220]. Balancing innovation with patient safety and ethical standards is crucial for the successful clinical implementation of these therapies.

Finally, as regulatory and ethical frameworks take shape, the production of exosomes for therapeutic purposes continues to face significant technical challenges, particularly in ensuring yield, purity, and consistency across various body fluids [223]. Differences in isolation methods—whether from blood, cerebrospinal fluid, urine, or saliva—contribute to variability in exosome quality, which in turn impacts their therapeutic efficacy [224]. Techniques such as ultracentrifugation, filtration, and immunoaffinity capture each have distinct advantages and limitations based on the fluid source, yet this variability underscores the need for a standardized, reproducible approach to exosome isolation [225]. Establishing such standardization would reduce costs, streamline procedures, and improve consistency, ultimately making exosome-based therapies more accessible and clinically viable [226]. Reaching a consensus on the most effective techniques to isolate high-quality exosomes with therapeutic potential from each fluid type is essential. Standardized protocols and rigorous testing will be crucial for optimizing exosome production to meet the demands of clinical application and ensure reliable patient outcomes.

In conclusion, exosomes derived from various body fluids present a transformative opportunity in the diagnosis and treatment of neurodegenerative diseases. Their unique ability to serve as non-invasive, accessible, and rapid biomarkers, coupled with their potential as targeted therapeutic delivery vehicles, positions exosomes as a critical tool in advancing personalized medicine. However, to realize this potential fully, challenges surrounding standardization, targeting specificity, regulatory pathways, and ethical considerations must be systematically addressed. Through collaborative research efforts, technological innovation, and the development of robust regulatory frameworks, exosome research can transition from bench to bedside, paving the way for more effective and accessible care for neurodegenerative disease patients. Continued investment in this area holds the promise of transforming patient outcomes and shaping the future of neurodegenerative disease management.

Current Challenges and Future Perspectives

Despite the promising potential of exosomes as both biomarkers and therapeutic agents in neurodegenerative diseases, significant challenges remain, including the standardization of isolation techniques, exosome heterogeneity, risk of immune activation, challenges in large-scale production for clinical applications, short circulation half-life, long-term safety, and the need for standardized regulatory frameworks for exosome-based therapeutics.

Firstly, the lack of standardized protocols for isolating and characterizing exosomes poses a fundamental challenge [227]. Current methods, such as ultracentrifugation and immunoaffinity capture, vary widely in terms of purity, yield, and exosomal integrity, leading to inconsistencies across studies and limiting reproducibility [228]. Secondly, exosome heterogeneity further complicates the therapeutic landscape [229]. Exosomes originating from different cell types exhibit varied molecular profiles, which hinders the identification of disease-specific biomarkers crucial for early diagnosis and targeted therapy [230]. Moreover, immune activation remains a significant concern, particularly in the context of allogeneic or engineered exosomes [231]. Although exosomes generally have a lower immunogenicity than synthetic nanoparticles, research has indicated that specific exosomal components, including RNA cargo and surface proteins, can elicit immune responses, potentially restricting their long-term therapeutic applications [178]. Additional research is required to reduce immunogenicity while maintaining therapeutic efficacy. Furthermore, scaling up exosome production for clinical applications appears to be a substantial obstacle. Strict control over batch-to-batch consistency, purity, and functional integrity is necessary for large-scale production, but current isolation techniques are challenging to implement [232]. The development of high-throughput, standardized manufacturing processes is necessary to facilitate clinical translation, as existing methods, such as ultracentrifugation and size-exclusion chromatography, are not readily scalable [233]. The short half-life of exosome-based therapies in circulation is another critical limitation that considerably affects their efficacy in delivering therapeutic cargo to target sites [234]. Studies have demonstrated that EVs derived from human platelets have a circulation half-life of approximately 5.5 h [235],

whereas systemically administered exosomes exist in the bloodstream for only about 2 h before being rapidly cleared [236]. Another issue diminishing the therapeutic efficacy of exosomes is their rapid clearance, which restricts the adequate duration of their interaction with their target tissues [237]. To overcome this limitation, strategies such as encapsulation within biomaterial-based carriers or surface modifications, have been proposed to increase the therapeutic potential of exosomes and extend their circulation time [238]. In this context, the combination of the liposomal formulations may provide benefit from established stability and controlled release properties, while engineered exosomes offer superior biocompatibility and endogenous targeting capabilities [239]. When it comes to the long-term safety, the stability of exosomes and their potential adverse effects address further evaluation [240]. Despite the fact that patient-specific exosomes improve biocompatibility, their production is still resource-intensive and scaling up remains challenging [241]. Additionally, it is necessary to establish standardized regulatory frameworks, as the current guidelines may not adequately address the distinctive characteristics of exosomes, necessitating modifications for clinical translation [242]. These above-mentioned interrelated issues highlight the necessity for ongoing innovation and collaboration within scientific, regulatory, and clinical domains to fully exploit the therapeutic promise of exosomes in NDDs.

On the other hand, prospects for exosome-based applications in NDDs are promising, driven by advances in microfluidic technologies, CRISPR/Cas system, next-generation sequencing (NGS), artificial intelligence (AI), bioengineering modifications, personalized exosome production, and the discovery of disease-specific biomarkers. Microfluidic technologies offer new pathways for efficient exosome isolation, allowing for high-purity separation directly from complex biological fluids and potentially paving the way for integrated diagnostic devices at point-of-care settings [243]. CRISPR/Cas system is guided by an engineered RNA which makes genetic improvements in faulty region of a DNA. For example, a research study reported successful epigenome editing using this method, demonstrating a reduction in BACE1 expression in an Alzheimer's disease model [244]. NGS and quantitative PCR are accelerating the discovery of disease-specific exosomal biomarkers by enabling precise molecular profiling of exosome cargo, including RNA and protein content; this profiling is crucial for early diagnosis and personalized monitoring of disease progression [245]. AI and machine learning (ML) further enhance the field by providing powerful tools for analyzing exosomal data, uncovering correlations within molecular profiles that may indicate disease stages or predict therapeutic outcomes [246]. Furthermore, these AI algorithms have been used as biomarker detectives, analyzing proteome signature to identify cancer-related exosomes [247]. Additionally,

bioengineering approaches, such as modifying exosome surface proteins or embedding specific ligands, are enhancing targeting specificity, allowing exosomes to deliver therapeutic molecules directly to affected neural cells, thereby minimizing off-target effects [12, 248]. Personalized exosome production also holds promise, as exosomes derived from patient-specific cells are more likely to achieve high biocompatibility and minimize immune response, supporting the growing interest in tailored therapeutic interventions [249]. Finally, with the discovery of disease-specific biomarkers, exosomes are expected to enable not only early and dynamic disease monitoring but also real-time evaluation of treatment efficacy, allowing clinicians to adjust as necessary to maximize therapeutic impact [250]. Collectively, these advancements indicate a future in which exosomes may facilitate a responsive and personalized precision medicine revolution, fundamentally transforming the diagnosis and treatment of neurodegenerative diseases.

Conclusion

To close the gap between diagnosis and treatment, exosomes have become game-changing instruments in the study of neurodegenerative diseases. Their exceptional capabilities to transport biomarkers specific to diseases and to traverse the blood–brain barrier render them priceless for precise early detection and treatment. Despite the promising results of both preclinical and clinical investigations, there are still obstacles to overcome before these discoveries may be implemented in the clinic. These include issues with standardization, scalability, and regulatory frameworks. Applications based on exosomes have the potential to change the way neurodegenerative diseases are managed, leading to better patient outcomes and a move towards precision medicine, by encouraging collaboration across disciplines and making use of recent advances in molecular biology and bioengineering.

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Declarations

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References

1. Gadhave DG, Sugandhi V V., Jha SK et al (2024) Neurodegenerative disorders: Mechanisms of degeneration and therapeutic approaches with their clinical relevance. Ageing Res Rev 99

2. Mitani T, Isikay S, Gezdirici A et al (2021) High prevalence of multilocus pathogenic variation in neurodevelopmental disorders in the Turkish population. Am J Hum Genet 108:1981–2005. https://doi.org/10.1016/j.ajhg.2021.08.009

3. De Pedro-Cuesta J, Martínez-Martín P, Rábano A et al (2016) Drivers: a biologically contextualized, cross-inferential view of the epidemiology of neurodegenerative disorders. Journal of Alzheimer's Disease 51:1003–1022. https://doi.org/10.3233/JAD-150884

4. Stephenson J, Nutma E, van der Valk P, Amor S (2018) Inflammation in CNS neurodegenerative diseases Immunology 154:204–219

5. Peng C, Trojanowski JQ, Lee VMY (2020) Protein transmission in neurodegenerative disease. Nat Rev Neurol 16:199–212

6. Wilson DM, Cookson MR, Van Den Bosch L et al (2023) Hallmarks of neurodegenerative diseases. Cell 186:693–714

7. Zheng JC, Chen S (2022) Translational neurodegeneration in the era of fast growing international brain research. Transl Neurodegener 11

8. Shusharina N, Yukhnenko D Botman S et al (2023) Modern methods of diagnostics and treatment of neurodegenerative diseases and depression. Diagnostics 13(3):573

9. Pardo-Moreno T, González-Acedo A, Rivas-Domínguez A et al (2022) Therapeutic approach to Alzheimer's disease: current treatments and new perspectives. Pharmaceutics 14(6):1117

10. Ruck T, Nimmerjahn F, Wiendl H et al (2022) Next-generation antibody-based therapies in neurology. Brain 145:1229–1241. https://doi.org/10.1093/brain/awab465

11. Li N, Cheng C, Wu D et al (2025) Immunofluorescent analysis of exosomes using a microchip filled with transparent antibody-conjugated beads for breast cancer liquid biopsy. Anal Chim Acta 1345:. https://doi.org/10.1016/j.aca.2025.343743

12. Hao Y, Su C, Liu X et al (2022) Bioengineered microglia-targeted exosomes facilitate Aβ clearance via enhancing activity of microglial lysosome for promoting cognitive recovery in Alzheimer's disease. Biomaterials Advances 136:. https://doi.org/10.1016/j.bioadv.2022.212770

13. Zhang L, Chen P, Chen T et al (2025) In vivo self-assembled siRNAs within small extracellular vesicles attenuate LRRK2-induced neurodegeneration in Parkinson's disease models. J Control Release 378:1139–1153. https://doi.org/10.1016/j.jconrel.2024.12.045

14. Silva RO, Haddad M, Counil H et al (2025) Exploring the potential of plasma and adipose mesenchymal stem cell-derived extracellular vesicles as novel platforms for neuroinflammation therapy. Journal of Controlled Release 377:880–898. https://doi.org/10.1016/j.jconrel.2024.11.060

15. Akers JC, Gonda D, Kim R et al (2013) Biogenesis of extracellular vesicles (EV): exosomes, microvesicles, retrovirus-like vesicles, and apoptotic bodies. J Neurooncol 113:1–11. https://doi.org/10.1007/s11060-013-1084-8

16. Xia R, Li M, Huang B (2024) A new strategy for drug delivery systems in oral diseases using stem cell-derived extracellular vesicles: review and new perspectives. Postgrad Med J. https://doi.org/10.1093/postmj/qgae187

17. Yadav Anita and Nandy A and SA and GS (2024) Exosome mediated cell-cell crosstalk in tissue injury and repair. In: Kloc Malgorzata and Kubiak JZ and HM (ed) Intercellular and Interorganellar Transfer and Communication in Biology and Medicine. Springer International Publishing, Cham, pp 249–297

18. Barranco I, Padilla L, Parrilla I et al (2019) Extracellular vesicles isolated from porcine seminal plasma exhibit different tetraspanin expression profiles. Sci Rep 9:. https://doi.org/10.1038/s41598-019-48095-3

19. Xie A, Cheng G, Wu J et al (2025) Highly BBB-permeable nanomedicine reverses neuroapoptosis and neuroinflammation to treat Alzheimer's disease. Biomaterials 312:122749. https://doi.org/10.1016/j.biomaterials.2024.122749

20. Xu FF, Liu Z, Fang XX et al (2025) Microglia-derived exosomal ciRS-7 mediates IL-17A effect of promoting neurodegeneration via miR-7 and SNCA targets in an experimental Parkinson's disease. Int Immunopharmacol 148:. https://doi.org/10.1016/j.intimp.2025.114089

21. Verma H, Kaur S, Jeeth P et al (2025) Understanding Aβ25–35 peptide altered exosomal proteome and associated pathways linked with the Alzheimer's disease pathogenesis using human neuroblastoma SH-SY5Y Cells. Metab Brain Dis 40:. https://doi.org/10.1007/s11011-024-01469-7

22. Yang C, Song Y, Luo M et al (2025) Exosomes-encapsulated biomimetic polydopamine carbon dots with dual-targeting effect alleviate motor and non-motor symptoms of Parkinson's disease via anti-neuroinflammation. Int J Biol Macromol 296:139724. https://doi.org/10.1016/j.ijbiomac.2025.139724

23. Sattarov R, Havers M, Orbjörn C et al (2024) Phosphorylated tau in cerebrospinal fluid-derived extracellular vesicles in Alzheimer's disease: a pilot study. Sci Rep 14:. https://doi.org/10.1038/s41598-024-75406-0

24. Jafari A, Karimabadi K, Rahimi A et al (2023) The emerging role of exosomal miRNAs as biomarkers for early cancer detection: a comprehensive literature review. Technol Cancer Res Treat 22

25. rezakhani L, Fekri K, Rostaminasab G, Rahmati S (2023) Exosomes: special nano-therapeutic carrier for cancers, overview on anticancer drugs. Medical Oncology 40

26. Rahmati S, Karimi H, Alizadeh M et al (2024) Prospects of plant-derived exosome-like nanocarriers in oncology and tissue engineering. Hum Cell 37:121–138

27. Fan L, Mao C, Hu X et al (2020) New insights into the pathogenesis of Alzheimer's disease. Front Neurol 10

28. Long JM, Holtzman DM (2019) Alzheimer disease: an update on pathobiology and treatment strategies. Cell 179:312–339

29. Mansueto S, Fusco G, De Simone A (2023) α-Synuclein and biological membranes: the danger of loving too much. Chem Commun 59:8769–8778. https://doi.org/10.1039/d3cc01682j

30. Xue J, Guo H, Gao Y et al (2019) Altered directed functional connectivity of the hippocampus in mild cognitive impairment

and Alzheimer's disease: a resting-state fMRI study. Front Aging Neurosci 11:. https://doi.org/10.3389/fnagi.2019.00326

31. Breijyeh Z, Karaman R (2020) Comprehensive review on Alzheimer's disease: causes and treatment. Molecules 25

32. Lanoiselée HM, Nicolas G, Wallon D et al (2017) APP, PSEN1, and PSEN2 mutations in early-onset Alzheimer disease: a genetic screening study of familial and sporadic cases. PLoS Med 14:. https://doi.org/10.1371/journal.pmed.1002270

33. Yamazaki Y, Zhao N, Caulfield TR et al (2019) Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. Nat Rev Neurol 15:501–518

34. Picca A, Calvani R, Coelho-Júnior HJ et al (2020) Mitochondrial dysfunction, oxidative stress, and neuroinflammation: intertwined roads to neurodegeneration. Antioxidants 9:1–21

35. Peeters G, Katelekha K, Lawlor B, Demnitz N (2022) Sex differences in the incidence and prevalence of young-onset Alzheimer's disease: a meta-analysis. Int J Geriatr Psychiatry 37

36. Atri A (2019) Current and future treatments in Alzheimer's disease. Semin Neurol 39:227–240. https://doi.org/10.1055/s-0039-1678581

37. Loera-Valencia R, Cedazo-Minguez A, Kenigsberg PA et al (2019) Current and emerging avenues for Alzheimer's disease drug targets. J Intern Med 286:398–437

38. Surmeier DJ (2018) Determinants of dopaminergic neuron loss in Parkinson's disease. FEBS J 285:3657–3668

39. Pang SYY, Ho PWL, Liu HF et al (2019) The interplay of aging, genetics and environmental factors in the pathogenesis of Parkinson's disease. Transl Neurodegener 8

40. Willard AM, Isett BR, Whalen T et al State transitions in the substantia nigra reticulata predict the onset of motor deficits in models of progressive dopamine depletion in mice. https://doi.org/10.7554/eLife.42746.001

41. Mahul-Mellier A-L, Burtscher J, Maharjan N et al The process of Lewy body formation, rather than simply α-synuclein fibrillization, is one of the major drivers of neurodegeneration. https://doi.org/10.6084/m9.figshare.11842389.v2

42. Hustad E, Aasly JO (2020) Clinical and imaging markers of prodromal Parkinson's disease. Front Neurol 11

43. Morgan JC, Fox SH Treating the motor symptoms of Parkinson disease

44. Tabrizi SJ, Ghosh R, Leavitt BR (2019) Huntingtin lowering strategies for disease modification in Huntington's disease. Neuron 101:801–819

45. Singh-Bains MK, Waldvogel HJ, Faull RLM (2016) The role of the human globus pallidus in Huntington's disease. Brain Pathol 26:741–751. https://doi.org/10.1111/bpa.12429

46. Baake V, Reijntjes RHAM, Dumas EM et al (2017) Cognitive decline in Huntington's disease expansion gene carriers. Cortex 95:51–62. https://doi.org/10.1016/j.cortex.2017.07.017

47. Krause A, Mitchell C, Essop F et al (2015) Junctophilin 3 (JPH3) expansion mutations causing Huntington disease like 2 (HDL2) are common in South African patients with African ancestry and a Huntington disease phenotype. Am J Med Genet B Neuropsychiatr Genet 168:573–585. https://doi.org/10.1002/ajmg.b.32332

48. Wilson H, Dervenoulas G, Politis M (2018) Structural magnetic resonance imaging in Huntington's disease. In: International Review of Neurobiology. Academic Press Inc., pp 335–380

49. Bono-Yagüe J, Gómez-Escribano AP, Millán JM, Vázquez-Manrique RP (2020) Reactive species in Huntington disease: are they really the radicals you want to catch? Antioxidants 9:1–35. https://doi.org/10.3390/antiox9070577

50. Coppen EM, Roos RAC (2017) Current pharmacological approaches to reduce chorea in Huntington's disease. Drugs 77:29–46

51. (2020) Autosomal dominant. In: Definitions. Qeios

52. Hoffmann D, Haapasalo A (2022) Patient-derived skin fibroblasts as a model to study frontotemporal lobar degeneration. Neural Regen Res 17:2669–2671. https://doi.org/10.4103/1673-5374.335814

53. Bottero V, Alrafati F, Santiago JA, Potashkin JA (2021) Transcriptomic and network meta-analysis of frontotemporal dementias. Front Mol Neurosci 14:. https://doi.org/10.3389/fnmol.2021.747798

54. Tamaki Y, Urushitani M (2022) Molecular dissection of TDP-43 as a leading cause of ALS/FTLD. Int J Mol Sci 23

55. Malpetti M, Rittman T, Jones PS et al (2021) In vivo PET imaging of neuroinflammation in familial frontotemporal dementia. J Neurol Neurosurg Psychiatry 92:319–322. https://doi.org/10.1136/jnnp-2020-323698

56. Li P, Quan W, Wang Z et al (2022) Early-stage differentiation between Alzheimer's disease and frontotemporal lobe degeneration: clinical, neuropsychology, and neuroimaging features. Front Aging Neurosci 14:. https://doi.org/10.3389/fnagi.2022.981451

57. Pottier C, Ravenscroft TA, Sanchez-Contreras M, Rademakers R (2016) Genetics of FTLD: overview and what else we can expect from genetic studies. J Neurochem 32–53

58. Liscic RM (2017) Als and Ftd: insights into the disease mechanisms and therapeutic targets. Eur J Pharmacol 817:2–6. https://doi.org/10.1016/j.ejphar.2017.10.012

59. Raffaele F, Claudia M, John H (2019) Genetics and molecular mechanisms of frontotemporal lobar degeneration: an update and future avenues. Neurobiol Aging 78:98–110

60. Oeckl P, Steinacker P, Feneberg E, Otto M (2015) Cerebrospinal fluid proteomics and protein biomarkers in frontotemporal lobar degeneration: current status and future perspectives. Biochim Biophys Acta Proteins Proteom 1854:757–768

61. Dick KM, Patterson K, Patricia Vázquez Rodríquez Fm et al (2016) Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes. https://doi.org/10.1212/WNL.0000000000002638

62. Mandić-Stojmenović G, Kostić V, Stefanova E (2018) The clinical spectrum of frontotemporal dementia. Medicinski podmladak 69:9–15. https://doi.org/10.5937/mp69-16325

63. Burk K, Pasterkamp RJ (2019) Disrupted neuronal trafficking in amyotrophic lateral sclerosis. Acta Neuropathol 137:859–877

64. (2019) Motor neuron diseases. In: Definitions. Qeios

65. Özoğuz A, Uyan Ö, Birdal G et al (2015) The distinct genetic pattern of ALS in Turkey and novel mutations. Neurobiol Aging 36:1764.e9-1764.e18. https://doi.org/10.1016/j.neurobiolaging.2014.12.032

66. Wang MD, Little J, Gomes J et al (2017) Identification of risk factors associated with onset and progression of amyotrophic lateral sclerosis using systematic review and meta-analysis. Neurotoxicology 61:101–130. https://doi.org/10.1016/j.neuro.2016.06.015

67. Masrori P, Van Damme P (2020) Amyotrophic lateral sclerosis: a clinical review. Eur J Neurol 27:1918–1929

68. Xu X, Shen D, Gao Y et al (2021) A perspective on therapies for amyotrophic lateral sclerosis: can disease progression be curbed? Transl Neurodegener 10

69. Paipa AJ, Povedano M, Barcelo A et al (2019) Survival benefit of multidisciplinary care in amyotrophic lateral sclerosis in Spain: association with noninvasive mechanical ventilation. J Multidiscip Healthc 12:465–470. https://doi.org/10.2147/JMDH.S205313

70. McKay KA, Smith KA, Smertinaite L et al (2021) Military service and related risk factors for amyotrophic lateral sclerosis. Acta Neurol Scand 143:39–50

71. Marin B, Boumé diene F, Logroscino G et al (2017) Variation in world wide incidence of amyotrophic lateral sclerosis: a

meta-analysis. Int J Epidemiol 46:57–74. https://doi.org/10.1093/ije/dyw061

72. Punjani R, Larson TC, Wagner L et al (2023) Survival and epidemiology of amyotrophic lateral sclerosis (ALS) cases in the Chicago and Detroit metropolitan cohort: incident cases 2009–2011 and survival through 2018. Amyotroph Lateral Scler Frontotemporal Degener 24:203–211. https://doi.org/10.1080/21678421.2022.2121167

73. Klockgether T, Mariotti C, Paulson HL (2019) Spinocerebellar ataxia. Nat Rev Dis Primers 5:. https://doi.org/10.1038/s41572-019-0074-3

74. Müller U (2021) Spinocerebellar ataxias (SCAs) caused by common mutations. Neurogenetics 22:235–250

75. Tonholo Silva TY, Rosa ABR, Quaio CR et al (2021) Does SCA45 cause very late-onset pure cerebellar ataxia? Neurol Genet 7:e581. https://doi.org/10.1212/NXG.0000000000000581

76. Coarelli G, Brice A, Durr A (2018) Recent advances in understanding dominant spinocerebellar ataxias from clinical and genetic points of view. F1000Res 7

77. Paulson HL, Shakkottai VG, Clark HB, Orr HT (2017) Polyglutamine spinocerebellar ataxias-from genes to potential treatments. Nat Rev Neurosci 18:613–626

78. De Mattei F, Ferrandes F, Gallone S et al (2024) Epidemiology of spinocerebellar ataxias in Europe. Cerebellum 23:1176–1183

79. Ramaglia V, Rojas O, Naouar I, Gommerman JL (2024) The ins and outs of central nervous system inflammation-lessons learned from multiple sclerosis. Annual Review of Immunology Downloaded from www.annualreviews.org Guest 01: https://doi.org/10.1146/annurev-immunol-093019

80. Gruchot J, Weyers V, Göttle P et al (2019) The molecular basis for remyelination failure in multiple sclerosis. Cells 8

81. Dobson R, Giovannoni G (2019) Multiple sclerosis – a review. Eur J Neurol 26:27–40

82. Walton C, King R, Rechtman L et al (2020) Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. Multiple Sclerosis Journal 26:1816–1821. https://doi.org/10.1177/1352458520970841

83. Lassmann H (2018) Multiple sclerosis pathology. Cold Spring Harb Perspect Med 8

84. Correale J, Marrodan M, Ysrraelit MC (2019) Mechanisms of neurodegeneration and axonal dysfunction in progressive multiple sclerosis. Biomedicines 7

85. Hemond CC, Bakshi R (2018) Magnetic resonance imaging in multiple sclerosis. Cold Spring Harb Perspect Med 8:. https://doi.org/10.1101/cshperspect.a028969

86. Mortensen GL, Rasmussen PV (2017) The impact of quality of life on treatment preferences in multiple sclerosis patients. Patient Prefer Adherence 11:1789–1796. https://doi.org/10.2147/PPA.S142373

87. Riederer F (2017) Ocrelizumab versus placebo in primary progressive multiple sclerosis. Journal fur Neurologie, Neurochirurgie und Psychiatrie 18:30–31

88. Vermöhlen V, Schiller P, Schickendantz S et al (2018) Hippotherapy for patients with multiple sclerosis: a multicenter randomized controlled trial (MS-HIPPO). Mult Scler J 24:1375–1382. https://doi.org/10.1177/1352458517721354

89. Korsukewitz C, Wiendl H (2024) Emerging trends and challenges in multiple sclerosis in Europe: rethinking classification and addressing COVID-19 impact. The Lancet Regional Health - Europe 44

90. Latifkar A, Hur YH, Sanchez JC et al (2019) New insights into extracellular vesicle biogenesis and function. J Cell Sci 132

91. Gangadaran P, Madhyastha H, Madhyastha R et al (2023) The emerging role of exosomes in innate immunity, diagnosis and therapy. Front Immunol 13

92. Gao P, Li X, Du X et al (2021) Diagnostic and therapeutic potential of exosomes in neurodegenerative diseases. Front Aging Neurosci 13

93. Zhang Y, Liu Y, Liu H, Tang WH (2019) Exosomes: biogenesis, biologic function and clinical potential. Cell Biosci 9

94. D'Anca M, Fenoglio C, Serpente M et al (2019) Exosome determinants of physiological aging and age-related neurodegenerative diseases. Front Aging Neurosci 11

95. Choi H, Choi K, Kim DH et al (2022) Strategies for targeted delivery of exosomes to the brain: advantages and challenges. Pharmaceutics 9

96. Nouri Z, Barfar A, Perseh S et al (2024) Exosomes as therapeutic and drug delivery vehicle for neurodegenerative diseases. J Nanobiotechnology 22:463. https://doi.org/10.1186/s12951-024-02681-4

97. Delila L, Nebie O, Le NTN et al (2024) Neuroprotective effects of intranasal extracellular vesicles from human platelet concentrates supernatants in traumatic brain injury and Parkinson's disease models. J Biomed Sci 31:. https://doi.org/10.1186/s12929-024-01072-z

98. Liu C, Wang J, Negishi R et al (2024) Label-free measurement of CD63 positive extracellular vesicles using terahertz chemical microscopy. ACS Sens 9:3244–3252. https://doi.org/10.1021/acssensors.4c00590

99. Shobeiri P, Alilou S, Jaberinezhad M et al (2023) Circulating long non-coding RNAs as novel diagnostic biomarkers for Alzheimer's disease (AD): a systematic review and meta-analysis. PLoS One 18:. https://doi.org/10.1371/journal.pone.0281784

100. Shu H, Zhang P, Gu L (2024) Alpha-synuclein in peripheral body fluid as a biomarker for Parkinson's disease. Acta Neurol Belg 124:831–842. https://doi.org/10.1007/s13760-023-02452-2

101. Juárez-Vaquera VH, Rosetti-Sciutto MF, Morales-Ruiz V, Adalid-Peralta L V. (2023) Meta-analysis to implement alpha-synuclein in extracellular vesicles as a potential biomarker for Parkinsons disease. Rev Invest Clin 75:193–202. https://doi.org/10.24875/RIC.23000017

102. Jang YO, Roh Y, Shin W et al (2024) Transferrin-conjugated magnetic nanoparticles for the isolation of brain-derived blood exosomal MicroRNAs: a novel approach for Parkinson's disease diagnosis. Anal Chim Acta 1306:. https://doi.org/10.1016/j.aca.2024.342623

103. Taha HB (2024) α-Synuclein in speculative neuronal extracellular vesicles: a marker for Parkinson's disease risk? Eur J Neurosci 60:4982–4986. https://doi.org/10.1111/ejn.16489

104. Tong MK, Thakur A, Yang T et al (2024) Amyloid-β oligomer-induced neurotoxicity by exosomal interactions between neuron and microglia. Biochem Biophys Res Commun 727:. https://doi.org/10.1016/j.bbrc.2024.150312

105. Fang X, Zhou D, Wang X et al (2024) Exosomes: a cellular communication medium that has multiple effects on brain diseases. Mol Neurobiol 61:6864–6892. https://doi.org/10.1007/s12035-024-03957-4

106. Ryu IS, Kim DH, Ro JY et al (2023) The microRNA-485–3p concentration in salivary exosome-enriched extracellular vesicles is related to amyloid β deposition in the brain of patients with Alzheimer's disease. Clin Biochem 118:. https://doi.org/10.1016/j.clinbiochem.2023.110603

107. Li Q, Liu H, Zhu Q et al (2024) Induction of tau pathology and motor dysfunction in mice by urinary exosomes from progressive supranuclear palsy patients. Brain Res Bull 216:111046. https://doi.org/10.1016/j.brainresbull.2024.111046

108. Zhyvolozhnyi A, Samoylenko A, Bart G et al (2024) Enrichment of sweat-derived extracellular vesicles of human and bacterial origin for biomarker identification. Nanotheranostics 8:48–63. https://doi.org/10.7150/ntno.87822

109. Östling J, Van Geest M, Olsson HK et al (2022) A novel non-invasive method allowing for discovery of pathologically relevant proteins from small airways. Clin Proteomics 19:. https://doi.org/10.1186/s12014-022-09348-y

110. Kaštelan S, Braš M, Pjevač N et al (2023) Tear biomarkers and Alzheimer's disease. Int J Mol Sci 24

111. Ananbeh H, Novak J, Juhas S et al (2022) Huntingtin co-isolates with small extracellular vesicles from blood plasma of TgHD and KI-HD pig models of Huntington's disease and human blood plasma. Int J Mol Sci 23:. https://doi.org/10.3390/ijms23105598

112. Bellini S, Saraceno C, Benussi L et al (2022) Plasma small extracellular vesicle cathepsin D dysregulation in GRN/C9orf72 and sporadic frontotemporal lobar degeneration. Int J Mol Sci 23:. https://doi.org/10.3390/ijms231810693

113. Singh R, Rai S, Bharti PS et al (2024) Circulating small extracellular vesicles in Alzheimer's disease: a case–control study of neuro-inflammation and synaptic dysfunction. BMC Med 22:. https://doi.org/10.1186/s12916-024-03475-z

114. Cheng YF, Gu XJ, Yang TM et al (2023) Signature of miRNAs derived from the circulating exosomes of patients with amyotrophic lateral sclerosis. Front Aging Neurosci 15:. https://doi.org/10.3389/fnagi.2023.1106497

115. Duan J, Lv A, Guo Z et al (2024) CX3CR1+/UCHL1+ microglial extracellular vesicles in blood: a potential biomarker for multiple sclerosis. J Neuroinflammation 21:254. https://doi.org/10.1186/s12974-024-03243-z

116. Jang YO, Ahn HS, Dao TNT et al (2023) Magnetic transferrin nanoparticles (MTNs) assay as a novel isolation approach for exosomal biomarkers in neurological diseases. Biomater Res 27:. https://doi.org/10.1186/s40824-023-00353-2

117. Dong Z, Gu H, Guo Q et al (2035) Profiling of serum exosome MiRNA reveals the potential of a MiRNA panel as diagnostic biomarker for Alzheimer's disease. https://doi.org/10.1007/s12035-021-02323-y/Published

118. Krishna G, Santhoshkumar R, Sivakumar PT et al (2023) Pathological (dis)similarities in neuronal exosome-derived synaptic and organellar marker levels between Alzheimer's disease and frontotemporal dementia. Journal of Alzheimer's Disease 94:S387–S397. https://doi.org/10.3233/JAD-220829

119. Jia L, Zhu M, Kong C et al (2021) Blood neuro-exosomal synaptic proteins predict Alzheimer's disease at the asymptomatic stage. Alzheimer's and Dementia 17:49–60. https://doi.org/10.1002/alz.12166

120. Soares Martins T, Marçalo R, da Cruz e Silva CB et al (2022) Novel exosome biomarker candidates for Alzheimer's disease unravelled through mass spectrometry analysis. Mol Neurobiol 59:2838–2854. https://doi.org/10.1007/s12035-022-02762-1

121. Trifunov S, Natera-De Benito D, Carrera-García L et al (2023) Full-length SMN transcript in extracellular vesicles as biomarker in individuals with spinal muscular atrophy type 2 treated with nusinersen. J Neuromuscul Dis 10:653–665. https://doi.org/10.3233/JND-230012

122. Otake K, Kamiguchi H, Hirozane Y (2019) Identification of biomarkers for amyotrophic lateral sclerosis by comprehensive analysis of exosomal mRNAs in human cerebrospinal fluid. BMC Med Genomics 12:7. https://doi.org/10.1186/s12920-019-0473-z

123. Hayashi N, Doi H, Kurata Y et al (2020) Proteomic analysis of exosome-enriched fractions derived from cerebrospinal fluid of amyotrophic lateral sclerosis patients. Neurosci Res 160:43–49. https://doi.org/10.1016/j.neures.2019.10.010

124. Hirschberg Y, Valle-Tamayo N, Dols-Icardo O et al (2023) Proteomic comparison between non-purified cerebrospinal fluid and cerebrospinal fluid-derived extracellular vesicles from patients with Alzheimer's, Parkinson's and Lewy body dementia. J Extracell Vesicles 12:. https://doi.org/10.1002/jev2.12383

125. Caron NS, Banos R, Aly AE et al (2022) Cerebrospinal fluid mutant huntingtin is a biomarker for huntingtin lowering in the striatum of Huntington disease mice. Neurobiol Dis 166:105652. https://doi.org/10.1016/j.nbd.2022.105652

126. Rani K, Rastogi S, Vishwakarma P et al (2021) A novel approach to correlate the salivary exosomes and their protein cargo in the progression of cognitive impairment into Alzheimer's disease. J Neurosci Methods 347:108980. https://doi.org/10.1016/j.jneumeth.2020.108980

127. Sun R, Wang H, Shi Y et al (2020) A pilot study of urinary exosomes in Alzheimer's disease. Neurodegener Dis 19:184–191. https://doi.org/10.1159/000505851

128. Song Z, Qu Y, Xu Y et al (2021) Microarray microRNA profiling of urinary exosomes in a 5XFAD mouse model of Alzheimer's disease. Animal Model Exp Med 4:233–242. https://doi.org/10.1002/ame2.12175

129. Song Z, Xu Y, Zhang L et al (2020) Comprehensive proteomic profiling of urinary exosomes and identification of potential non-invasive early biomarkers of Alzheimer's disease in 5XFAD mouse model. Front Genet 11:. https://doi.org/10.3389/fgene.2020.565479

130. Pieragostino D, Lanuti P, Cicalini I et al (2019) Proteomics characterization of extracellular vesicles sorted by flow cytometry reveals a disease-specific molecular cross-talk from cerebrospinal fluid and tears in multiple sclerosis. J Proteomics 204:. https://doi.org/10.1016/j.jprot.2019.103403

131. Zhang L, Lin J, Xiang K et al (2024) Omnidirectional improvement of mitochondrial health in Alzheimer's disease by multi-targeting engineered activated neutrophil exosomes. Journal of Controlled Release 376:470–487. https://doi.org/10.1016/j.jconrel.2024.10.033

132. Ye J, Sun X, Jiang Q et al (2024) Umbilical cord blood-derived exosomes attenuate dopaminergic neuron damage of Parkinson's disease mouse model. Journal of Nanobiotechnology 22:. https://doi.org/10.1186/s12951-024-02773-1

133. Reza-Zaldivar EE, Hernández-Sapiéns MA, Gutiérrez-Mercado YK et al (2019) Mesenchymal stem cell-derived exosomes promote neurogenesis and cognitive function recovery in a mouse model of Alzheimer's disease. Neural Regen Res 14:1626–1634. https://doi.org/10.4103/1673-5374.255978

134. Huang W, Lin M, Yang C et al (2021) Rat bone mesenchymal stem cell-derived exosomes loaded with miR-494 promoting neurofilament regeneration and behavioral function recovery after spinal cord injury. Oxid Med Cell Longev 2021:. https://doi.org/10.1155/2021/1634917

135. Xu Y, Zhu Z, huan, Xu X, et al (2023) Neuron-derived exosomes promote the recovery of spinal cord injury by modulating nerve cells in the cellular microenvironment of the lesion area. Mol Neurobiol 60:4502–4516. https://doi.org/10.1007/s12035-023-03341-8

136. Liu H, Jin M, Ji M et al (2022) Hypoxic pretreatment of adipose-derived stem cell exosomes improved cognition by delivery of circ-Epc1 and shifting microglial M1/M2 polarization in an Alzheimer's disease mice model. Aging 14:3070–3083. https://doi.org/10.18632/aging.203989

137. Hao Y, Su C, Liu X et al (2022) Bioengineered microglia-targeted exosomes facilitate Aβ clearance via enhancing activity of microglial lysosome for promoting cognitive recovery in Alzheimer's disease. Biomaterials Advances 136:212770. https://doi.org/10.1016/j.bioadv.2022.212770

138. Yao S, Wang Y, Tang Q et al (2024) A plug-and-play monofunctional platform for targeted degradation of extracellular proteins and vesicles. Nat Commun 15:. https://doi.org/10.1038/s41467-024-51720-z

139. Sánchez-Rubio M, Abarzúa-Catalán L, del Valle A et al (2024) Maternal stress during pregnancy alters circulating

small extracellular vesicles and enhances their targeting to the placenta and fetus. Biol Res 57:70. https://doi.org/10.1186/s40659-024-00548-4

140. Liu J, Zhao H, Gao T et al (2024) Glypican-3-targeted macrophages delivering drug-loaded exosomes offer efficient cytotherapy in mouse models of solid tumours. Nature Communications 15:. https://doi.org/10.1038/s41467-024-52500-5

141. Yadav J, Chaudhary A, Tripathi T et al (2024) Exosomal transcript cargo and functional correlation with HNSCC patients' survival. BMC Cancer 24:1144. https://doi.org/10.1186/s12885-024-12759-9

142. Collado A, Gan L, Tengbom J et al (2023) Extracellular vesicles and their non-coding RNA cargos: emerging players in cardiovascular disease. J Physiol 601:4989–5009. https://doi.org/10.1113/JP283200/support-information-section

143. Lee S-T, Im W, Ban J-J et al (2017) Exosome-based delivery of miR-124 in a Huntington's disease model. J Mov Disord 10:45–52. https://doi.org/10.14802/jmd.16054

144. Zheng X, Sun K, Liu Y et al (2023) Resveratrol-loaded macrophage exosomes alleviate multiple sclerosis through targeting microglia. J Control Release 353:675–684. https://doi.org/10.1016/j.jconrel.2022.12.026

145. Wang C-C, Hu X-M, Long Y-F et al (2024) Treatment of Parkinson's disease model with human umbilical cord mesenchymal stem cell-derived exosomes loaded with BDNF. Life Sci 356:123014. https://doi.org/10.1016/j.lfs.2024.123014

146. Izco M, Blesa J, Schleef M et al (2019) Systemic exosomal delivery of shRNA minicircles prevents Parkinsonian pathology. Mol Ther 27:2111–2122. https://doi.org/10.1016/j.ymthe.2019.08.010

147. Jiang P, Xiao Y, Hu X et al (2024) RVG29 peptide-modified exosomes loaded with Mir-133b mediate the RhoA-ROCK pathway to improve motor and neurological symptoms in Parkinson's disease. ACS Biomater Sci Eng 10:3069–3085. https://doi.org/10.1021/acsbiomaterials.3c01622

148. Hao Y, Su C, Liu X et al (2022) Bioengineered microglia-targeted exosomes facilitate Aβ clearance via enhancing activity of microglial lysosome for promoting cognitive recovery in Alzheimer's disease. Biomaterials Advances 136:212770. https://doi.org/10.1016/j.bioadv.2022.212770

149. Jahangard Y, Monfared H, Moradi A et al (2020) Therapeutic effects of transplanted exosomes containing miR-29b to a rat model of Alzheimer's disease. Front Neurosci 14:. https://doi.org/10.3389/fnins.2020.00564

150. Hosseini Shamili F, Alibolandi M, Rafatpanah H et al (2019) Immunomodulatory properties of MSC-derived exosomes armed with high affinity aptamer toward mylein as a platform for reducing multiple sclerosis clinical score. J Control Release 299:149–164. https://doi.org/10.1016/j.jconrel.2019.02.032

151. Joshi BS, Youssef SA, Bron R et al (2021) DNAJB6b-enriched small extracellular vesicles decrease polyglutamine aggregation in in vitro and in vivo models of Huntington disease. iScience 24:103282. https://doi.org/10.1016/j.isci.2021.103282

152. Chen Y-S, Harn H-J, Hong Z-X et al (2023) Preconditioning of exosomes derived from human olfactory ensheathing cells improved motor coordination and balance in an SCA3/MJD mouse model: a new therapeutic approach. Eur J Pharm Sci 191:106608. https://doi.org/10.1016/j.ejps.2023.106608

153. Tang Z, Hu S, Wu Z, He M (2023) Therapeutic effects of engineered exosome-based miR-25 and miR-181a treatment in spinocerebellar ataxia type 3 mice by silencing ATXN3. Mol Med 29:96. https://doi.org/10.1186/s10020-023-00695-6

154. Giunti D, Marini C, Parodi B et al (2021) Role of miRNAs shuttled by mesenchymal stem cell-derived small extracellular vesicles in modulating neuroinflammation. Sci Rep 11:1740. https://doi.org/10.1038/s41598-021-81039-4

155. Turner NP (2024) Playing pin-the-tail-on-the-protein in extracellular vesicle (EV) proteomics. Proteomics. https://doi.org/10.1002/pmic.202400074

156. Zhao H, Li Z, Liu D et al (2024) PlexinA1 (PLXNA1) as a novel scaffold protein for the engineering of extracellular vesicles. J Extracell Vesicles 13:. https://doi.org/10.1002/jev2.70012

157. Klyachko NL, Haney MJ, Lopukhov A V., Le-Deygen IM (2024) Cationized extracellular vesicles for gene delivery. Sci Rep 14:. https://doi.org/10.1038/s41598-024-75985-y

158. Kong Y (2022) Exosome-encapsulated miRNAs as protective agents against Huntington's disease. International Journal of High School Research 4:110–114. https://doi.org/10.36838/v4i4.21

159. Zhou R, Guo J, Jin Z (2024) Advancing osteoarthritis therapy with GMOCS hydrogel-loaded BMSCs-exos. J Nanobiotechnology 22:. https://doi.org/10.1186/s12951-024-02713-z

160. Choi H, Choi Y, Yim HY et al (2021) Biodistribution of exosomes and engineering strategies for targeted delivery of therapeutic exosomes. Tissue Eng Regen Med 18:499–511

161. Zheng W, Zhu T, Tang L et al (2023) Inhalable CAR-T cell-derived exosomes as paclitaxel carriers for treating lung cancer. J Transl Med 21:. https://doi.org/10.1186/s12967-023-04206-3

162. Yu Y, Li W, Mao L et al (2021) Genetically engineered exosomes display RVG peptide and selectively enrich a neprilysin variant: a potential formulation for the treatment of Alzheimer's disease. J Drug Target 29:1128–1138. https://doi.org/10.1080/1061186X.2021.1929257

163. Xu M, Feng T, Liu B et al (2021) Engineered exosomes: desirable target-tracking characteristics for cerebrovascular and neurodegenerative disease therapies. Theranostics 11:8926–8944

164. Hikita T, Miyata M, Watanabe R, Oneyama C (2020) In vivo imaging of long-term accumulation of cancer-derived exosomes using a BRET-based reporter. Sci Rep 10:. https://doi.org/10.1038/s41598-020-73580-5

165. Bano R, Soleja N, Mohd M (2023) Genetically encoded FRET-based nanosensor for real-time monitoring of A549 exosomes: early diagnosis of cancer. Anal Chem 95:5738–5746. https://doi.org/10.1021/acs.analchem.2c05774

166. Jung KO, Kim YH, Chung SJ et al (2020) Identification of lymphatic and hematogenous routes of rapidly labeled radioactive and fluorescent exosomes through highly sensitive multimodal imaging. Int J Mol Sci 21:1–16. https://doi.org/10.3390/ijms21217850

167. Hu WJ, Wei H, Cai LL et al (2024) Magnetic targeting enhances the neuroprotective function of human mesenchymal stem cell-derived iron oxide exosomes by delivering miR-1228-5p. J Nanobiotechnology 22:665. https://doi.org/10.1186/s12951-024-02941-3

168. Chen Z, Wu S, Sheng S et al (2025) hUCMSC-derived exosomes mitigate blood-spinal cord barrier disruption by activating AMPK/mTOR-mediated autophagic flux after acute spinal cord injury. Compos B Eng 289:111944. https://doi.org/10.1016/j.compositesb.2024.111944

169. Li C, Qin S, Wen Y et al (2022) Overcoming the blood-brain barrier: exosomes as theranostic nanocarriers for precision neuroimaging. Journal of Controlled Release 349:902–916. https://doi.org/10.1016/j.jconrel.2022.08.002

170. Mentor S, Fisher D (2022) Exosomes form tunneling nanotubes (TUNTs) in the blood-brain barrier: a nano-anatomical perspective of barrier genesis. Front Mol Neurosci 15:. https://doi.org/10.3389/fnmol.2022.938315

171. Salimi L, Seyedaghamiri F, Karimipour M et al (2023) Physiological and pathological consequences of exosomes at the blood–brain-barrier interface. Cell Communication and Signaling 21

172. Kim J, Zhu Y, Chen S et al (2023) Anti-glioma effect of ginseng-derived exosomes-like nanoparticles by active

173. Heidarzadeh M, Gürsoy-Özdemir Y, Kaya M et al (2021) Exosomal delivery of therapeutic modulators through the blood–brain barrier; promise and pitfalls. Cell Biosci 11

174. Wu D, Chen Q, Chen X et al (2023) The blood–brain barrier: structure, regulation, and drug delivery. Signal Transduct Target Ther 8

175. Huang LY, Song JX, Cai H et al (2022) Healthy serum-derived exosomes improve neurological outcomes and protect blood–brain barrier by inhibiting endothelial cell apoptosis and reversing autophagy-mediated tight junction protein reduction in rat stroke model. Front Cell Neurosci 16:. https://doi.org/10.3389/fncel.2022.841544

176. Tang N, Gong XR, Huang H, Meng Q (2023) Activated neutrophil-derived exosomes contribute to blood–brain barrier damage and hemorrhagic transformation after cerebral ischemia/reperfusion. Brain Res 1810:. https://doi.org/10.1016/j.brainres.2023.148374

177. Wang C, Cheng F, Han Z et al (2025) Human-induced pluripotent stem cell–derived neural stem cell exosomes improve blood–brain barrier function after intracerebral hemorrhage by activating astrocytes via PI3K/AKT/MCP-1 axis. Neural Regen Res 20:518–532. https://doi.org/10.4103/nrr.nrr-d-23-01889

178. Akhlaghpasand M, Tavanaei R, Hosseinpoor M et al (2024) Safety and potential effects of intrathecal injection of allogeneic human umbilical cord mesenchymal stem cell-derived exosomes in complete subacute spinal cord injury: a first-in-human, single-arm, open-label, phase I clinical trial. Stem Cell Res Ther 15:. https://doi.org/10.1186/s13287-024-03868-0

179. Chen YA, Lu CH, Ke CC et al (2021) Mesenchymal stem cell-derived exosomes ameliorate Alzheimer's disease pathology and improve cognitive deficits. Biomedicines 9:. https://doi.org/10.3390/biomedicines9060594

180. Virla F, Turano E, Scambi I et al (2024) Administration of adipose-derived stem cells extracellular vesicles in a murine model of spinal muscular atrophy: effects of a new potential therapeutic strategy. Stem Cell Res Ther 15:. https://doi.org/10.1186/s13287-024-03693-5

181. Lee M, Liu T, Im W, Kim M (2016) Exosomes from adipose-derived stem cells ameliorate phenotype of Huntington's disease in vitro model. Eur J Neurosci 44:2114–2119. https://doi.org/10.1111/ejn.13275

182. Bonafede R, Scambi I, Peroni D et al (2016) Exosome derived from murine adipose-derived stromal cells: neuroprotective effect on in vitro model of amyotrophic lateral sclerosis. Exp Cell Res 340:150–158. https://doi.org/10.1016/j.yexcr.2015.12.009

183. Xie X, Song Q, Dai C et al (2023) Clinical safety and efficacy of allogenic human adipose mesenchymal stromal cells-derived exosomes in patients with mild to moderate Alzheimer's disease: a phase I/II clinical trial. Gen Psychiatr 36:. https://doi.org/10.1136/gpsych-2023-101143

184. Al Abdullah S, Cocklereece I, Dellinger K (2024) Unlocking the potential of circulating small extracellular vesicles in neurodegenerative disease through targeted biomarkers and advancements in biosensing. Exploration of BioMat-X 1:100–123. https://doi.org/10.37349/ebmx.2024.00008

185. Alzahrani FA, Riza YM, Eid TM et al (2024) Exosomes in vascular/neurological disorders and the road ahead. Cells 13

186. Kim KY, Shin KY, Chang KA (2024) Potential exosome biomarkers for Parkinson's disease diagnosis: a systematic review and meta-analysis. Int J Mol Sci 25

187. Xu X, Iqbal Z, Xu † Limei, et al (2024) Brain-derived extracellular vesicles: potential diagnostic biomarkers for central nervous system diseases PCN Psychiatry and Clinical Neurosciences. Psychiatry Clin Neurosci 78:83–96. https://doi.org/10.1111/pcn.13610/full

188. Rasouli A, Roshangar L, Hosseini M et al (2024) Beyond boundaries: the therapeutic potential of exosomes in neural microenvironments in neurological disorders. Neuroscience 553:98–109

189. Wu Z, Qiao Z, Chen S et al (2024) Interstitial fluid-based wearable biosensors for minimally invasive healthcare and biomedical applications. Commun Mater 5

190. Haghayegh F, Norouziazad A, Haghani E et al (2024) Revolutionary point-of-care wearable diagnostics for early disease detection and biomarker discovery through intelligent technologies. Advanced Science

191. Arslan B, Zetterberg H, Ashton NJ (2024) Blood-based biomarkers in Alzheimer's disease – moving towards a new era of diagnostics. Clin Chem Lab Med 62:1063–1069. https://doi.org/10.1515/cclm-2023-1434

192. Marjani AA, Nader ND, Aghanejad A (2024) Exosomes as targeted diagnostic biomarkers: recent studies and trends. Life Sci 354:122985. https://doi.org/10.1016/j.lfs.2024.122985

193. Yin H, You S, Li X et al (2024) Progress, challenges, and prospects of small extracellular vesicles isolation and characterization. Journal of Holistic Integrative Pharmacy 5:121–130. https://doi.org/10.1016/j.jhip.2024.06.001

194. Yakubovich EI, Polischouk AG, Evtushenko VI (2022) Principles and problems of exosome isolation from biological fluids. Biochem (Mosc) Suppl Ser A Membr Cell Biol 16:115–126

195. Fotuhi SN, Khalaj-Kondori M, Ali M et al (2019) Long noncoding RNA BACE1-AS may serve as an Alzheimer's disease blood-based biomarker. https://doi.org/10.1007/s12031-019-01364-2/Published

196. Feng L, Liao YT, He JC et al (2018) Plasma long non-coding RNA BACE1 as a novel biomarker for diagnosis of Alzheimer disease. BMC Neurol 18:. https://doi.org/10.1186/s12883-017-1008-x

197. Liu CG, Zhao Y, Lu Y, Wang PC (2021) ABCA1-labeled exosomes in serum contain higher microRNA-193b levels in Alzheimer's disease. Biomed Res Int 2021:. https://doi.org/10.1155/2021/5450397

198. Shen J, Ma Z, Xu J et al (2024) Exosome isolation and detection: from microfluidic chips to nanoplasmonic biosensor. ACS Appl Mater Interfaces 16:22776–22793. https://doi.org/10.1021/acsami.3c19396

199. Sharma V, Nikolajeff F, Kumar S (2023) Employing nanoparticle tracking analysis of salivary neuronal exosomes for early detection of neurodegenerative diseases. Transl Neurodegener 12

200. Wei J, Qi T, Hao C et al (2023) Optical microscopic and spectroscopic detection of exosomes. TrAC Trends in Analytical Chemistry 163:117077. https://doi.org/10.1016/j.trac.2023.117077

201. Zeng X, Wu C, Xiong Y et al (2024) Target proteins-regulated DNA nanomachine-electroactive substance complexes enable separation-free electrochemical detection of clinical exosome. Biosens Bioelectron 256:116273. https://doi.org/10.1016/j.bios.2024.116273

202. Wu Y, Wu Z, Xu W et al (2024) A label-free colorimetric biosensor utilizing natural material for highly sensitive exosome detection. Talanta 275:126182. https://doi.org/10.1016/j.talanta.2024.126182

203. Kulkarni M, Kar R, Ghosh S et al (2024) Clinical impact of multi-omics profiling of extracellular vesicles in cancer liquid biopsy. The Journal of Liquid Biopsy 3:100138. https://doi.org/10.1016/j.jlb.2024.100138

204. Mun B, Jeong H, Kim R et al (2024) 3D-Nanostructured microfluidic device arranged in a herringbone pattern for the highly effective capture of HER2-Positive cancer-derived exosomes in

urine. Chemical Engineering Journal 482:148851. https://doi.org/10.1016/j.cej.2024.148851

205. Barrettino D, Zumbuhl C, Kummer R et al (2023) Low-cost portable medical device for the detection and quantification of exosomes. In: 2023 IEEE SENSORS. pp 1–4

206. Chu L, Sun Y, Zhao Y et al (2024) Exosome-mediated delivery platform of biomacromolecules into the brain: cetuximab in combination with doxorubicin for glioblastoma therapy. Int J Pharm 660:124262. https://doi.org/10.1016/j.ijpharm.2024.124262

207. Bahadorani M, Nasiri M, Dellinger K et al (2024) Engineering exosomes for therapeutic applications: decoding biogenesis, content modification, and cargo loading strategies. Int J Nanomedicine 19:7137–7164

208. Deng R, Wu J, Zhu B et al (2024) Engineered exosomes loaded with M1–8 peptide for targeted therapy of hepatocellular carcinoma. Appl Mater Today 37:. https://doi.org/10.1016/j.apmt.2024.102071

209. Zhao J, Cui X, Zhan Q et al (2024) CRISPR-Cas9 library screening combined with an exosome-targeted delivery system addresses tumorigenesis/TMZ resistance in the mesenchymal subtype of glioblastoma. Theranostics 14:2835–2855. https://doi.org/10.7150/thno.92703

210. McAndrews KM, Xiao F, Chronopoulos A et al (2021) Exosome-mediated delivery of CRISPR/Cas9 for targeting of oncogenic KrasG12D in pancreatic cancer. Life Sci Alliance 4:. https://doi.org/10.26508/LSA.202000875

211. Su N, Zhang J, Liu W et al (2025) Specific isolation and quantification of PD-L1 positive tumor derived exosomes for accurate breast cancer discrimination via aptamer-functionalized magnetic composites and SERS immunoassay. Talanta 281:126956. https://doi.org/10.1016/j.talanta.2024.126956

212. Ellipilli S, Wang H, Binzel DW et al (2023) Ligand-displaying-exosomes using RNA nanotechnology for targeted delivery of multi-specific drugs for liver cancer regression. Nanomedicine 50:102667. https://doi.org/10.1016/j.nano.2023.102667

213. Yuan S, Li Q, He C et al (2024) Anti-BCMA–engineered exosomes for bortezomib-targeted delivery in multiple myeloma. Blood Adv 8:4886–4899. https://doi.org/10.1182/bloodadvances.2023012464

214. Yang Q, Liu G, Chen G et al (2024) Novel injectable adhesive hydrogel loaded with exosomes for holistic repair of hemophilic articular cartilage defect. Bioact Mater 42:85–111. https://doi.org/10.1016/j.bioactmat.2024.08.018

215. Mu S, Qian T, Li Z et al (2024) Long-term storage and intradermal vaccination of tumor-derived exosomes via sugar microneedles for improving tumor immunotherapies. Chemical Engineering Journal 497:155595. https://doi.org/10.1016/j.cej.2024.155595

216. Shetgaonkar GG, Marques SM, DCruz CEM, et al (2022) Exosomes as cell-derivative carriers in the diagnosis and treatment of central nervous system diseases. Drug Deliv Transl Res 12:1047–1079

217. Jiang C, Hopfner F, Katsikoudi A et al (2020) Serum neuronal exosomes predict and differentiate Parkinson's disease from atypical parkinsonism. J Neurol Neurosurg Psychiatry 91:720–729. https://doi.org/10.1136/jnnp-2019-322588

218. Zhang L, Lin J, Xiang K et al (2024) Omnidirectional improvement of mitochondrial health in Alzheimer's disease by multi-targeting engineered activated neutrophil exosomes. J Control Release 376:470–487. https://doi.org/10.1016/j.jconrel.2024.10.033

219. Stapleton S (2020) Exosomes as therapeutics and drug delivery vehicles: global regulatory perspectives. Cell Gene Ther Insights 6:1561–1569. https://doi.org/10.18609/cgti.2020.172

220. Lener T, Gimona M, Aigner L et al (2015) Applying extracellular vesicles based therapeutics in clinical trials - an ISEV position paper. J Extracell Vesicles 4:. https://doi.org/10.3402/jev.v4.30087

221. Rezaie J, Feghhi M, Etemadi T (2022) A review on exosomes application in clinical trials: perspective, questions, and challenges. Cell Communication and Signaling 20

222. Batrakova E V, Kim MS (2016) Development and regulation of exosome-based therapy products. WIREs Nanomedicine and Nanobiotechnology 8:744–757. https://doi.org/10.1002/wnan.1395

223. Omrani M, Beyrampour-Basmenj H, Jahanban-Esfahlan R et al (2024) Global trend in exosome isolation and application: an update concept in management of diseases. Mol Cell Biochem 479:679–691

224. Williams S, Fernandez-Rhodes M, Law A et al (2023) Comparison of extracellular vesicle isolation processes for therapeutic applications. J Tissue Eng 14:. https://doi.org/10.1177/20417314231174609

225. Pammi Guru KT, Praween N, Basu PK (2023) Isolation of exosomes from human serum using gold-nanoparticle-coated silicon surface. Nanomaterials 13:. https://doi.org/10.3390/nano13030387

226. Panwar D, Shrivastava D, Bhawal S et al (2023) Detection of exosomes in various biological fluids utilizing specific epitopes and directed multiple antigenic peptide antibodies. Rev Anal Chem 42:. https://doi.org/10.1515/revac-2023-0056

227. Yadav A, Xuan Y, Sen CK, Ghatak S (2024) Standardized reporting of research on exosomes to ensure rigor and reproducibility. Adv Wound Care (New Rochelle) 13:584–599. https://doi.org/10.1089/wound.2024.0093

228. Rai A, Fang H, Fatmous M et al (2021) A protocol for isolation, purification, characterization, and functional dissection of exosomes. In: Posch A (ed) Proteomic Profiling: Methods and Protocols. Springer, US, New York, NY, pp 105–149

229. Wu D, Sun H, Yang B et al (2024) Exosome heterogeneity affects the distal "barrier-crossing" trafficking of exosome encapsulated quantum dots. ACS Nano 18:7907–7922. https://doi.org/10.1021/acsnano.3c09378

230. Sancho-Albero M, Navascués N, Mendoza G, et al. (2019) Exosome origin determines cell targeting and the transfer of therapeutic nanoparticles towards target cells. J Nanobiotechnology 17:. https://doi.org/10.1186/s12951-018-0437-z

231. Yang M, Pu L, Yang S et al (2024) Engineered antler stem cells derived exosomes potentiate anti-tumor efficacy of immune checkpoint inhibitor by reprogramming immunosuppressive tumor microenvironment. Chemical Engineering Journal 479:. https://doi.org/10.1016/j.cej.2023.147421

232. Ma CY, Zhai Y, Li CT et al (2024) Translating mesenchymal stem cell and their exosome research into GMP compliant advanced therapy products: promises, problems and prospects. Med Res Rev 44:919–938

233. Thakur A, Rai D (2024) Global requirements for manufacturing and validation of clinical grade extracellular vesicles. The Journal of Liquid Biopsy 6:100278. https://doi.org/10.1016/j.jlb.2024.100278

234. Wang D, Bai Y, Cheng G et al (2024) Exosome-drug conjugates delivery: a promising strategy for ameliorating the pharmacokinetic profile of artesunate. Front Bioeng Biotechnol 12:. https://doi.org/10.3389/fbioe.2024.1437787

235. Rank A, Nieuwland R, Crispin A et al (2011) Clearance of platelet microparticles in vivo. Platelets 22:111–116. https://doi.org/10.3109/09537104.2010.520373

236. Takahashi Y, Nishikawa M, Shinotsuka H et al (2013) Visualization and in vivo tracking of the exosomes of murine melanoma

B16-BL6 cells in mice after intravenous injection. J Biotechnol 165:77–84. https://doi.org/10.1016/j.jbiotec.2013.03.013

237. Parada N, Romero-Trujillo A, Georges N, Alcayaga-Miranda F (2021) Camouflage strategies for therapeutic exosomes evasion from phagocytosis. J Adv Res 31:61–74

238. Shahzad KA, Wang Z, Li X et al (2024) Immunomodulatory effect of PLGA-encapsulated mesenchymal stem cells-derived exosomes for the treatment of allergic rhinitis. Front Immunol 15:. https://doi.org/10.3389/fimmu.2024.1429442

239. Liu Y, Li M, Gu J et al (2025) Engineering of exosome-liposome hybrid-based theranostic nanomedicines for NIR-II fluorescence imaging-guided and targeted NIR-II photothermal therapy of subcutaneous glioblastoma. Colloids Surf B Biointerfaces 245:. https://doi.org/10.1016/j.colsurfb.2024.114258

240. Wang Y, Huo Y, Zhao C et al (2024) Engineered exosomes with enhanced stability and delivery efficiency for glioblastoma therapy. Journal of Controlled Release 368:170–183. https://doi.org/10.1016/j.jconrel.2024.02.015

241. Chandran NS, Bhupendrabhai MN, Tan TT et al (2025) A phase 1, open-label study to determine safety and tolerability of the topical application of mesenchymal stem/stromal cell (MSC) exosome ointment to treat psoriasis in healthy volunteers. Cytotherapy. https://doi.org/10.1016/j.jcyt.2025.01.007

242. Wang CK, Tsai TH, Lee CH (2024) Regulation of exosomes as biologic medicines: regulatory challenges faced in exosome development and manufacturing processes. Clin Transl Sci 17

243. Park M, Lee CH, Noh H et al (2025) High-precision extracellular-vesicle isolation-analysis integrated platform for rapid cancer diagnosis directly from blood plasma. Biosens Bioelectron 267:. https://doi.org/10.1016/j.bios.2024.116863

244. Han J, Sul JH, Lee J et al (2025) Engineered exosomes with a photoinducible protein delivery system enable CRISPR-Cas–based epigenome editing in Alzheimer's disease. Sci Transl Med 16:eadi4830. https://doi.org/10.1126/scitranslmed.adi4830

245. Wang Q, Wang H, Zhao X et al. (2024) Transcriptome sequencing of circular RNA reveals the involvement of hsa-SCMH1_0001 in the pathogenesis of Parkinson's disease. CNS Neurosci Ther 30:. https://doi.org/10.1111/cns.14435

246. Greenberg ZF, Graim KS, He M (2023) Towards artificial intelligence-enabled extracellular vesicle precision drug delivery. Adv Drug Deliv Rev 199

247. Li B, Kugeratski FG, Kalluri R (2024) A novel machine learning algorithm selects proteome signature to specifically identify cancer exosomes. Elife 12:RP90390: https://doi.org/10.7554/eLife

248. Lopes D, Lopes J, Pereira-Silva M et al (2023) Bioengineered exosomal-membrane-camouflaged abiotic nanocarriers: neurodegenerative diseases, tissue engineering and regenerative medicine. Mil Med Res 10

249. Zhang J, Zhao Y, Hu H et al (2025) A colorimetric nano-enzyme assay with Ni@Pt nanoparticles as signal labels for rapid and sensitive detection of exosomal Aβ42 in plasma. Microchimica Acta 192:. https://doi.org/10.1007/s00604-024-06862-8

250. Orefice NS, Souchet B, Braudeau J et al (2019) Real-time monitoring of exosome enveloped-AAV spreading by endomicroscopy approach: a new tool for gene delivery in the brain. Mol Ther Methods Clin Dev 14:237–251. https://doi.org/10.1016/j.omtm.2019.06.005