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Advances in Nanotechnology - Engineered Exosomes for Early Biomarker Detection and Therapy in Alzheimer's Disease

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Abstract: *Advances in the understanding of exosome biology have led to their recognition as the heart of intercellular communications. Additionally, the new insights into the role of exosomes in neuroinflammation and spreading of characteristic Alzheimer's Disease (AD) pathologies, open the scope for their use as a key target for diagnostic and therapeutic innovation. The immuno-engineering platforms are sensitive for detecting exosomal biomarkers including amyloid- β species, phosphorylated tau, and regulatory microRNAs, in peripheral biofluids with minimal invasion. Hence, these are potential platforms that can facilitate early diagnosis of AD. Although most supporting evidence is presently derived based on preclinical models and limited observational cohorts, these findings support minimally invasive opportunities for early disease monitoring and diagnosis, possibly even before the manifestation of clinical symptoms of AD. Alongside, another advantage of engineered exosomes is their flexible framework for targeted drug delivery. Since engineered exosomes are derived from neuronal or mesenchymal stem cells, they can cross the blood-brain barrier and deliver neuroprotective or immunomodulatory agents with high specificity. Presently, the target precision and off-target biodistribution of engineered exosomes are one of the most active areas of investigation. More encouragingly, incorporating nanotechnology for surface modification and cargo loading strategies can further enhance exosomal signaling, delivery efficiency, and cell-specific uptake by neuronal and glial cells. These applications, however, are presently challenging in terms of scalability and reproducibility. Also, a number of advancements are needed in areas of standardization of exosome isolation, scalable manufacturing, regulatory frameworks, and biological heterogeneity. Overcoming these challenges, however, is feasible with the integration of Artificial Intelligence and multi-omics profiling, and optimisation of exosome-based interventions.*

Keywords: *engineered exosomes; nanotechnology; multi-omics; Alzheimer's disease; neuronal targeting.*

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1. Introduction

The nanosized extracellular vesicles (30–150 nm) produced by the endosomal mechanism have attracted the attention of researchers in recent years as pathological mediators and possible therapeutic tools for the management of Alzheimer's Disease (AD) (Lakshmi et al., 2020; Zhao et al., 2023). These vesicles are promising biomarkers since they carry proteins, lipids, and nucleic acids that reflect the physiological and pathological conditions of their parent cells, are capable of crossing the blood–brain barrier (BBB), and can be detected in peripheral biofluids (Song et al., 2020). In AD pathogenesis, disease progression is characterised by spreading of misfolded amyloid β (A β) peptides and hyperphosphorylated tau proteins between cells through exosomes, which amplify neurodegenerative signalling cascades (Lakshmi et al., 2020; Zhao et al., 2023; Chen et al., 2017). This places brain-derived exosomes at an intersection as a mediator of disease propagation and a potential biomarker. With the help of nanoimmunoengineering, an interdisciplinary field that combines nanotechnology and immunology principles and applications, it is now possible to devise strong strategies to modulate exosomal pathways (Chuang et al., 2022). In the field of diagnostics, nanoscale biosensors, immunoaffinity platforms, and microfluidic devices allow detection of highly sensitive exosome-associated biomarkers in liquid biopsies (Hsu & Wu, 2022; Marassi et al., 2023). This further allows early and minimally invasive disease assessment in AD. From a therapeutic dimension, engineered exosomes are promising biocompatible carrier systems capable of transporting drugs, nucleic acids, or antibodies across the BBB. They also offer opportunities for targeted modulation of the neuroinflammatory microenvironment in preclinical models (Vani et al., 2025; Premchandani et al., 2025; Mehdizadeh et al., 2025). In this mini-review, we explore the advances in understanding exosomal pathways in AD, their interactions with immune systems, and the impact of nanoimmunoengineering strategies on early detection and therapeutic modulation of AD.

2. Exosomal Pathways in Alzheimer's Disease

2.1. Exosome Biology and Cargo: Pathological Roles in Amyloid, Tau, and Inflammation

Exosomes are nanosized extracellular vesicles (30–150 nm) generated through an endosomal lysosomal pathway. They are released by all cell types, including neurons, astrocytes, oligodendrocytes, and microglia (Figure 1) (Zhao et al., 2023). The exosome's cargo reflects the parent cell's physiological or pathological condition and carries specific amyloid precursor protein (APP), tau protein, lipids, messenger RNAs and microRNAs (Park et al., 2024; Chen et al., 2019; Kapogiannis et al., 2014). This allows the exosomes to function as active mediators of intercellular communication within the brain microenvironment. Evidence shows that exosomes transport pathological amyloid- β (A- β) peptides as well as hyperphosphorylated tau proteins across the BBB, thereby contributing to amyloid plaque formation and neurofibrillary tangle propagation (Lakshmi et al., 2020). Tau-containing exosomes are released from affected neurons and spread along neuroanatomically connected brain regions, with various cell types such as microglia contributing to tauopathy progression (Pérez et al., 2019). The activated microglia-derived exosome can also amplify inflammatory cascades, while dysfunctional neuronal cell-derived exosomes can act as damage signals to unveil further glial attack (Lukiw & Pogue, 2020; Li et al., 2022). Collectively, these episodes exacerbate disease progression in AD (Lakshmi et al., 2020; Park et al., 2024; Kapogiannis et al., 2014; Pérez et al., 2019; Lukiw & Pogue, 2020; Li et al., 2022).

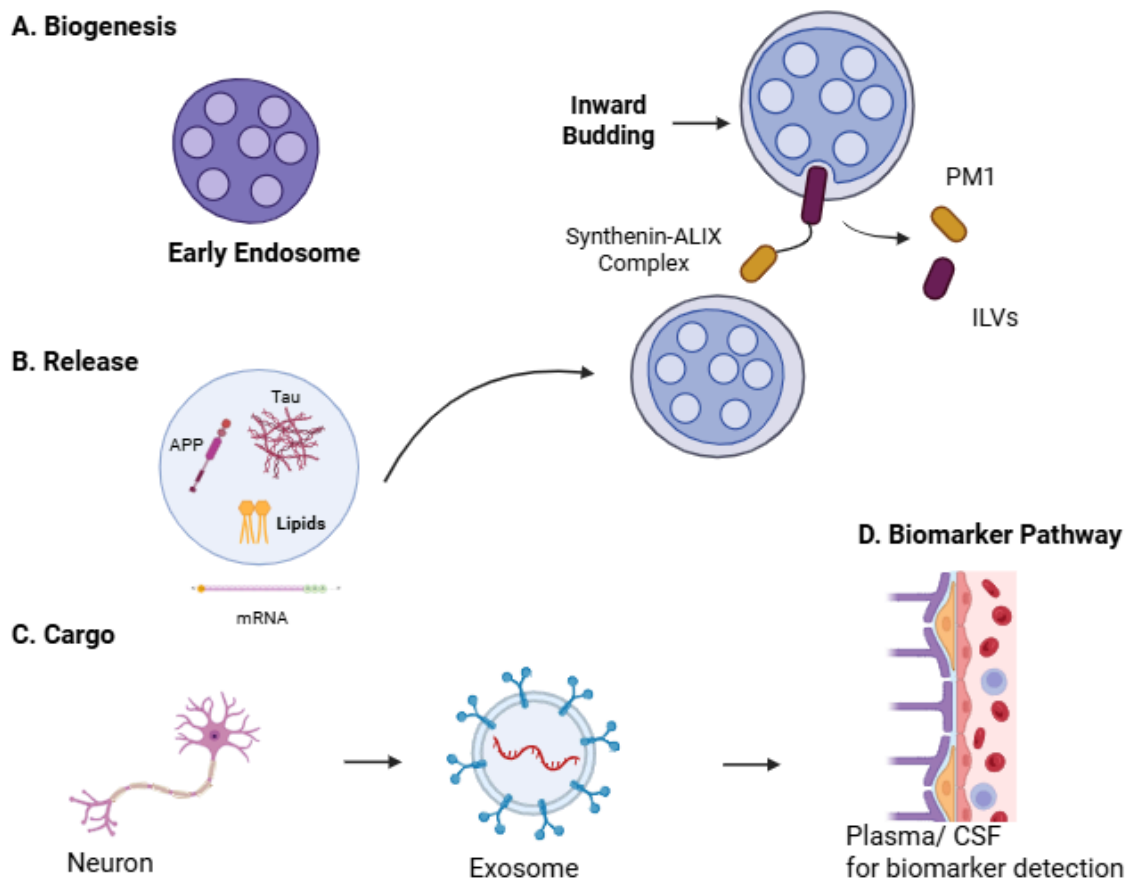


Figure 1: Exosome Biogenesis, Release, and Biomarker Potential in Alzheimer's Disease
MVBs : Multivesicular Bodies; PM1: Particulate Matter 1; mRNA: Messenger RNA; CSF : cerebrospinal fluid; ILVs: Intraluminal Vesicles.

2.2. Diagnostic Potential of Circulating Exosomes

Notably, neuronal exosomes are able to cross the BBB, enabling the detection of their molecular content, which includes neurodegeneration-associated proteins and nucleic acids, in peripheral biofluids, including plasma, serum, and cerebrospinal fluid (CSF) (Zhao et al., 2023; Park et al., 2024; Li et al., 2022; Saeedi et al., 2019). Hence, they have the potential to emerge as the most promising biomarker for AD, which can be detected with minimally invasive methods (Jiang et al., 2019). Elevated levels of exosomal A β 42, phosphorylated tau, and neurofilament light chain have been reported in neuron-specific exosomes derived from plasma. Based on these key findings, several studies have demonstrated a correlation between the stage of the disease and cognitive impairment (Winston et al., 2016). More precisely, considerably increased concentrations of phosphorylated tau (P-T181-tau, P-S396-tau) and A β 42 are consistently reported in neurally derived exosomes from AD patients compared to healthy controls (Winston et al., 2016; Fiandaca et al., 2015). Some longitudinal studies suggest that the exosomal biomarkers can act as potential indicators of future development of AD by preceding onset of clinical symptoms by up to 10 years. These studies also suggest accurate differentiation of AD patients from controls with high specificity using exosome-based diagnosis (Winston et al., 2016; Fiandaca et al., 2015). Similarly, exosomal microRNAs, such as miR-193b, miR-146a, and miR-29, have been linked to synaptic dysfunction, inflammation, and amyloid metabolism. These insights offer multiplexed signatures for the diagnosis of AD (Chen et al., 2017; Siedlecki-Wullich et al., 2021). Compared to conventional biomarkers, exosomes provide a stable and protective environment for their molecular cargo,

enhancing sensitivity in early disease detection through liquid biopsy approaches in clinical practice (Soares Martins et al., 2021).

3. Exosome–Immune System Interactions in Alzheimer's Disease

3.1. Exosomal Regulation of Neuroinflammation

Substantial evidence-based studies suggest that exosomes can modulate and enhance the cycles of neuroinflammation by transporting danger-associated molecular patterns (DAMPs), components of activated NF- κ B pathways, and inflammatory microRNAs such as miR-146a and miR-155. The immunological effects of exosomes are highly dependent on their cellular origin and molecular cargo. For instance, circulating exosomes from lipopolysaccharide-challenged mice have been reported to induce microglial activation and astrogliosis in recipient mice, leading to upregulation of inflammatory microRNAs such as miR-155 (Li et al., 2018; Pascual et al., 2020). Conversely, exosomes derived from regulatory immune cells or stem cells are reported to exhibit strong anti-inflammatory properties. The observed suppression of inflammation occurs due to the transmission of immunoregulatory factors such as TGF- β or miR-124 to glial cells (Riazifar et al., 2019; Du et al., 2018; Heo et al., 2020). More specifically, mesenchymal stem cell (MSC)-derived exosomes may create an anti-inflammatory environment through the upregulation of cytokines IL-10 and TGF β 1 while downregulating other proinflammatory mediators such as IL-6, IL-12p70, IL17AF, and IL-22 (Riazifar et al., 2019; Du et al., 2018). In the same way, melatonin-stimulated MSC-derived exosomes deliver anti-inflammatory microRNAs like miR-34a, miR-124 and miR-135b to further suppress inflammation (Heo et al., 2020). The capacity of exosomes to amplify or suppress neuroinflammatory signalling makes their functional plasticity within the immune landscape of AD.

3.2. Opportunities for Immunomodulatory Targeting

Several novel pathways for therapeutic immunomodulation have been proposed in recent years, given the central role of exosomes in neuroimmune communication (Weng et al., 2022; Han et al., 2025). The major cellular sources of exosomes and their immunomodulatory roles in AD are summarised in Table 1. As reported in Table 1, exosome-based therapeutic strategies in Alzheimer's disease originate from distinct cellular sources, including neurons, glial cells, mesenchymal stem cells, and peripheral immune cells. Table 1 is intended to provide a high-level functional overview of these exosome sources rather than a detailed depiction of underlying molecular mechanisms, which are discussed in the main text. In this context, mesenchymal stem cell-derived exosomes exert prominent immunomodulatory and neuroprotective effects through the transfer of anti-inflammatory cargos such as miR-29b, miR-124, IL-10, and TGF- β , contributing to microglial reprogramming and suppression of pro-inflammatory signalling pathways. Importantly, engineered and hybrid exosomes, explicitly listed in Table 1, represent the translational extension of these naturally derived vesicles, reflecting a shift from descriptive characterisation of endogenous exosomes toward functional optimisation for targeted delivery, immunomodulation, and enhanced blood–brain barrier transport. Rather than constituting a separate category, engineered exosomes should be viewed as modified derivatives of the cellular exosome sources outlined in Table 1. Engineering strategies preserve the intrinsic biological identity of parent cell-derived exosomes while enhancing their therapeutic performance through surface functionalization, cargo enrichment, and targeting ligand incorporation. This conceptual progression establishes engineered exosomes as a logical extension of endogenous exosome biology rather than a distinct platform. The advancement in exosome engineering has further enabled surface modification with brain-homing peptides as well as highly efficient loading of neuroprotective agents, gene-editing tools, and anti-inflammatory molecules (Premchandani et al., 2025). Compared to synthetic carriers, engineered exosomes have lower immunogenicity and can also be functionalised further with immunoregulatory ligands to elicit a precise therapeutic effect (Premchandani et al., 2025; Jain et

al., 2025). These modifications allow these bioengineered platforms to modulate key inflammatory signalling mechanisms involved in AD pathology, including NF- κ B, JAK/STAT, and MAPK pathways. The engineered exosomes carrying anti-inflammatory molecules, immune checkpoint regulators, or microRNAs capable of reprogramming dysfunctional microglial cells have shown promise in counteracting chronic inflammation in patients with AD (Han et al., 2025). A significant example is represented by the engineered exosomes containing miR-29b-2, functionalised with targeting ligands like somatostatin and immune evasion proteins such as CD47. When intravenously administered, these exosomes can successfully decrease presenilin-1 expression and β -amyloid accumulation in AD mouse models (Lin et al., 2024). In addition, miR-29b-loaded exosomes have been found to prevent spatial learning and memory deficits in A β -treated rats via downregulation of BACE1 and BIM target genes (Jahangard et al., 2020). Despite persistent difficulties related to scalable producibility and standardisation, nanoimmunoengineering strategies functionalizing exosomes with immunoregulatory ligands are a very promising pathway to shift immune responses from neurotoxic to neuroprotective orientation (Chuang et al., 2022; Premchandani et al., 2025; Li et al., 2019; Pi et al., 2021).

Table 1. Cellular sources of exosomes and their functional roles in Alzheimer's disease

#	Exosome sources	Cargo components	Functional role in AD	Advantages	Limitations
1	Neuronal-derived exosomes	A β , phosphorylated tau, APP fragments, miRNAs	Propagation of amyloid and tau pathology and disease-specific biomarkers	High CNS and disease specificity	Low abundance in peripheral fluids and isolation complexity
Lakshmi et al., 2020; Zhao et al., 2023; Pérez et al., 2019; Winston et al., 2016					
2	Microglial-derived exosomes	Cytokines, miR-155, inflammatory mediators	Amplification of neuroinflammation	Reflect immune activation status	Potentially proinflammatory effects
Lukiw & Pogue, 2020; Li et al., 2022; Li et al., 2018; Pascual et al., 2020					
3	Astrocyte-derived exosomes	Lipids, A β -associated proteins, metabolic enzymes	Regulation of neuroinflammation and modulation of A β metabolism	Abundant CNS source; metabolic support	Lower disease specificity
Park et al., 2024; Kapogiannis et al., 2014					
4	Oligodendrocyte-derived exosomes	Myelin proteins, metabolic regulators	Axonal support and intercellular metabolic coupling	Supports neuronal integrity	Limited direct AD-specific evidence
Zhao et al., 2023; Park et al., 2024					
5	Mesenchymal stem cell-derived exosomes	miR-124, miR-29b, TGF- β , IL-10	Neuroprotection, immunomodulation and therapeutic delivery	Low immunogenicity; therapeutic potential	Cargo heterogeneity and scalability challenges
Riazifar et al., 2019; Du et al., 2018; Heo et al., 2020					
6	Peripheral immune cell-derived exosomes	Cytokines, immune signalling molecules	Links systemic inflammation with CNS pathology	Accessible in circulation	Indirect CNS specificity
Li et al., 2018					
7	Engineered / hybrid exosomes	Therapeutic RNAs, drugs, targeting ligands	Targeted delivery, immunomodulation and BBB transport	High versatility and precision targeting	Manufacturing, standardisation and regulation
Premchandani et al., 2025; Jain et al., 2025; Lin et al., 2024; Kandimalla et al., 2023; Mushtaq et al., 2025; Huang et al., 2020; Smith & Waterman, 1981; Iyaswamy et al., 2023					

4. Nano-Immunoengineering Strategies

4.1. Nanotechnology for Modulating Exosomal Signalling

Nanotechnology-engineered exosomes represent a targeted drug delivery system that can divert natural signalling pathways to play a twofold role in AD, from that of a mediator of disease to a carrier vehicle for therapies (Kandimalla et al., 2023). Exosomes may be engineered to behave like small molecules and macromolecules across the BBB. This can serve to deliver amyloid-beta modulators, which were demonstrated in preclinical studies to reduce A β accumulation and neuroinflammation (Mushtaq et al., 2025). Advanced hybrid nanostructures such as Lipid-dendrimer-calcium phosphate (LDPC) nanoparticles have been engineered to perform dual targeted immunogene therapy. These nanoparticles engage with exosome-associated signalling mechanisms, and directly modulate key molecular pathways implicated in AD progression (Huang et al., 2020; Smith & Waterman, 1981). Similarly, Fe65 engineered neuronal exosomes can deliver corynoxine-B, an autophagy inducer, to amyloid precursor protein (APP) overexpressing neurons, thereby blocking the pathological Fe65-APP interaction (Iyaswamy et al., 2023). Besides serving as cargo delivery vehicles, these nanotechnological approaches facilitate the targeted modulation of exosomal crosstalk between neurons and glial cells, thereby promoting the release and transport of neuroprotective factors such as brain-derived neurotrophic factor (BDNF) (Xia et al., 2021).

4.2. Immunoengineering Approaches for Early Detection

Advances in immunoengineering have enabled ultrasensitive exosome biomarker detection for the development of minimally invasive tools for early diagnosis of AD. Platforms like Toppan's Digital ICA™ use high-sensitivity fluorescence for the identification of exosomes carrying glycolipid GM1 bound by A β leaked from the brain, even at extremely low concentrations (Yuyama et al., 2022; Hu et al., 2024). A β -bound extracellular vesicles carrying ganglioside GM1 can be quantitatively detected using the immunodigital invasive cleavage techniques. This assay correlates with the level of A β accumulation in the brain of an AD mouse model (Yuyama et al., 2022). Complementary microfluidic methods use drop-shaped porous chips conjugated with rolling circle amplification to accomplish highly sensitive detection of exosomal A β 42 and p-tau181 proteins via fluorescence quantification (Xu et al., 2025). These ultrasensitive detection technologies for single-molecule arrays are used to simultaneously determine several plasma biomarkers, thereby increasing diagnostic accuracy for early AD detection (Álvarez-Sánchez et al., 2022).

4.3. Engineered Exosomal Pathways for Therapeutic Intervention

Engineered exosomes have been proposed as a promising platform for targeted therapy in AD due to their inherent ability to cross the BBB (Vani et al., 2025; Kudpaje et al., 2025). By surface modification and ligand-receptor engineering, exosomes will be able to specifically couple with neuronal cells, promoting efficient endocytosis and precise delivery of therapeutic cargo such as small molecules, proteins, or genetic materials (Premchandani et al., 2025; Kudpaje et al., 2025). This targeted approach overcomes the challenge of BBB penetration and enhances drug accumulation at disease sites and therefore ensures minimised off-target effects in peripheral organs (Premchandani et al., 2025; Vani et al., 2025; Yang, 2025; Mehdizadeh et al., 2025). Engineered exosomes can retain intrinsic functional molecules while delivering additional neuroprotective agents. This property can significantly amplify the therapeutic efficacy of engineered exosomes (Dehghani et al., 2025; Chen et al., 2024). Within this framework, the engineered exosome strategies summarised in Table 2 reflect distinct but complementary translational objectives, including enhancement of brain-specific delivery, modulation of amyloid and tau pathology, activation of autophagic pathways, and reprogramming of neuroinflammatory responses. MicroRNA-loaded exosomes primarily aim to restore dysregulated gene networks implicated in AD

progression, whereas surface-functionalized and immune-evasive exosomes are designed to address pharmacokinetic limitations such as rapid systemic clearance and insufficient brain accumulation. Rather than serving as a descriptive listing, Table 2 provides a comparative overview of how specific engineering choices, cargo selection, and targeting strategies influence mechanistic outcomes and therapeutic performance across preclinical models.

An overview of nanoimmunoengineered exosome platforms, therapeutic cargo, and targeted pathways evaluated in preclinical AD models is presented in Table 2. It should be noted that the experimental models summarised in Table 2 encompass a heterogeneous spectrum, including in vitro neuronal systems, transgenic mouse models, and toxin- or peptide-induced rodent models. While this diversity reflects the multifactorial nature of Alzheimer's disease and enables mechanistic exploration of distinct pathological pathways, it also influences translational interpretation. In vitro models primarily capture cell-autonomous effects and cargo-specific mechanisms, whereas animal models differ in their ability to recapitulate amyloid deposition, tau pathology, neuroinflammation, and cognitive decline. Consequently, therapeutic outcomes observed across these models are not directly comparable and should be interpreted within the context of the specific pathological features each model represents. Careful model selection is therefore essential when extrapolating preclinical efficacy of engineered exosome strategies toward clinical relevance in Alzheimer's disease.

Table 2. Engineered exosome-based therapeutic strategies in preclinical models of Alzheimer's disease

Sr. No.	Engineering strategy	Therapeutic cargo	Target pathway / mechanism	Experimental model	Outcomes
1	Targeted exosomes with immune-evasion ligands	miR-29b-2	Presenilin-1 regulation and A β reduction	AD mouse model	Decrease in A β burden and improved pathology
Lin et al., 2024					
2	Neuronal Fe65-engineered exosomes	Corynoxine-B	Autophagy induction and Fe65-APP disruption	APP-overexpressing neurons	Decreased pathological APP processing
Iyaswamy et al., 2023					
3	MSC-derived exosomes	miR-124, miR-29b	Microglial reprogramming and anti-inflammatory signalling	AD rodent models	Decreased IL-6 and improved IL-10 levels leading to neuroprotection
Riazifar et al., 2019; Du et al., 2018; Heo et al., 2020					
4	Melatonin-stimulated MSC exosomes	miR-34a, miR-124, miR-135b	Suppression of neuroinflammation	AD mouse model	Decreased microglial activation
Heo et al., 2020					
5	Brain-homing peptide-modified exosomes	Anti-A β agents	BBB penetration and targeted delivery	Preclinical AD models	Reduced A β deposition
Premchandani et al., 2025; Mushtaq et al., 2025					
6	CD47-functionalised exosomes	Therapeutic RNAs	Immune evasion and prolonged circulation	AD mouse model	Increased brain uptake and reduced clearance
Lin et al., 2024; Kandimalla et al., 2023					
7	Astrocyte-derived engineered exosomes	Neurotrophic factors	Synaptic support and A β metabolism	In vitro / rodent models	Increased neuronal survival
Park et al., 2024; Xia et al., 2021					

4.4. Challenges and Future Perspectives

Exosomal nanotechnology represents one of the most recent and dynamic fields in nanomedicine; however, the rapid advancements are associated with major challenges that must be addressed before the nanoimmunoengineered hybrids can achieve clinical translation. Technical

challenges include the standardisation of exosome isolation methods, ensuring scalability of production, and achieving reproducibility across batches (Jangam et al., 2025; Sharma et al., 2024; Tian et al., 2023; Lee et al., 2025). Safety issues involve possible immunological reactions and unintended biological effects (Jangam et al., 2025; Tian et al., 2023). From a translational perspective, the exosome-based nanomedicine regulatory frameworks have not been well articulated, particularly with respect to FDA guidelines towards exosome-based therapeutics (Sharma et al., 2024). Looking forward, artificial intelligence (AI) combined with multi-omics profiling will likely expedite the discovery of exosomal biomarkers, while hybrid nanomaterial-exosome systems will play an important role in stability and targeting accuracy. These innovations will determine whether exosome-centred nanoimmunoengineering can fulfil its potential and enable earlier diagnosis, personalised interventions, and potentially disease-modifying therapies.

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