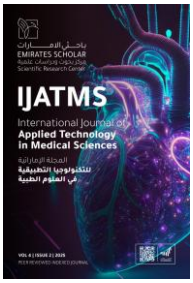

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Translational applications of exosomal proteomics in personalised medicine: using detailed proteomic analysis of exosomes to develop individualised therapeutic strategies.

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ABSTRACT

Exosomal proteomics is becoming an indispensable asset in the advancement of personalised medicine, offering a non-invasive means of disease characterisation, biomarker identification, and therapy customisation. Exosomes - nanoscale extracellular vesicles secreted by nearly all cell types, encapsulate a complex cargo of proteins, lipids, metabolites, and nucleic acids that mirror the physiological or pathological condition of their cellular origin. Among these, the proteomic constituents offer critical insight into intracellular pathways, rendering them highly valuable for elucidating disease mechanisms and tailoring molecularly informed treatments. Recent innovations in mass spectrometry-based proteomic technologies have refined the ability to decode disease-specific exosomal protein signatures, enabling early-stage diagnosis and real-time monitoring via liquid biopsies, especially in oncology. Additionally, exosomes are being investigated as next-generation therapeutic vehicles, engineered to deliver targeted biomolecules with high biocompatibility and minimal immunogenicity. Despite ongoing challenges in isolation standardisation, cargo heterogeneity, and clinical scalability, progress in exosome engineering and proteomic analytics continues to unlock new possibilities. The integration of exosomal proteomics into clinical practice marks a transformative shift towards precision medicine, where treatment strategies are increasingly aligned with individual molecular profiles. Exosomal proteomics is becoming an indispensable asset in the advancement of personalised medicine, offering a non-invasive means of disease characterisation, biomarker identification, and therapy customisation. Exosomes - nanoscale extracellular vesicles secreted by nearly all cell types, encapsulate a complex cargo of proteins, lipids, metabolites, and nucleic acids that mirror the physiological or pathological condition of their cellular origin. Among these, the proteomic constituents offer critical insight into intracellular pathways, rendering them highly valuable for elucidating disease mechanisms and tailoring molecularly informed treatments. Recent innovations in mass spectrometry-based proteomic technologies have refined the ability to decode disease-specific exosomal protein signatures, enabling early-stage diagnosis and real-time monitoring via liquid biopsies, especially in oncology. Additionally, exosomes are being investigated as next-generation therapeutic vehicles, engineered to deliver targeted biomolecules with high biocompatibility and minimal immunogenicity. Despite ongoing challenges in isolation standardisation, cargo heterogeneity, and clinical scalability, progress in exosome engineering and proteomic analytics continues to unlock new possibilities. The integration of exosomal proteomics into clinical practice marks a transformative shift towards precision medicine, where treatment strategies are increasingly aligned with individual molecular profiles.

Keywords: *Exosomal Proteomics*, *Personalised Medicine Strategies*, *Exosome-Based Therapeutics*, *Proteomic Biomarkers in Precision Medicine*, *Translational Exosome Research*.

1. An Introduction to Exosomal Proteomics within the Framework of Personalised Medicine

Personalised medicine marks a paradigm shift in healthcare by moving beyond the traditional "one-size-fits-all" model to a more precise, individualised approach that incorporates a patient's genetic profile, environmental exposure, and lifestyle factors. This shift aims to enhance therapeutic efficacy, reduce adverse drug reactions, and improve overall patient outcomes (*Pandey & Gupta, 2024; Parmar et al., 2021*). At the heart of this transformation lie integrative technologies such as high-throughput sequencing, bioinformatics, and systems biology, which enable the identification of disease-specific molecular signatures and actionable targets (*Qian et al., 2024*; Knowledge, Attitude and Ethical Perception towards precision Medicine Among Healthcare Professionals, 2024).

Despite its transformative potential, personalised medicine still grapples with substantial challenges. The discovery and clinical validation of composite biomarkers that reliably predict treatment responses remain limited by tumour heterogeneity, genetic complexity, and resistance mechanisms (Ahmed, 2024; Foroutan, 2015). Additionally, ethical, regulatory, and economic considerations, such as data privacy, accessibility of advanced diagnostics, and health equity, continue to hinder its widespread adoption (Dharani & Kamaraj, 2024; Siddique, 2024).

Whereas conventional therapeutic strategies derive efficacy from standardised clinical trial models, personalised medicine emphasises the development of predictive, preventive, and participatory care, particularly by leveraging advancements in omics technologies. In this context, proteomics has emerged as a particularly powerful tool. As proteins serve as both functional effectors and disease biomarkers, proteomic profiling provides a dynamic reflection of the physiological state and molecular pathology of individual patients (Simonian, 2016; Vasdev, 2020). Unlike genomics, which identifies potential predispositions, proteomics captures real-time cellular processes, protein-protein interactions, and post-translational modifications that are often central to disease progression and therapeutic resistance (*Guest et al., 2013*; Proteomics in Human Healthcare, 2022).

When integrated with genomics and metabolomics, proteomics enhances the resolution of disease phenotyping and enables the stratification of patients into more refined therapeutic categories. Recent applications include the identification of diagnostic and prognostic biomarkers in neurodegenerative diseases, such as Alzheimer's disease, and in malignancies where dysregulated protein networks are mapped to tailor treatment protocols (*Ryu et al., 2025; Hegde et al., 2024*). Moreover, proteomic technologies such as liquid chromatography-tandem mass spectrometry (LC-MS/MS) and multiplexed assays have facilitated the translation of biomarker discovery into clinical practice (Wilson, 2004; Steinmetz, 2022).

Within this proteomic landscape, exosomal proteomics has garnered growing interest due to the unique characteristics of exosomes - nanoscale extracellular vesicles actively secreted into biofluids, including blood, urine, and cerebrospinal fluid. These vesicles encapsulate proteins, lipids, and nucleic acids reflective of their parent cells, making them ideal candidates for non-invasive liquid biopsies in cancer and other systemic diseases (*Yu et al., 2022; Panfoli et al., 2022*). Exosomes are inherently stable, biocompatible, and capable of traversing biological barriers, thus offering a multifaceted platform for diagnostics, monitoring, and targeted therapy (Silva, 2022; Sharrer, 2023).

The therapeutic potential of exosomes extends beyond their diagnostic capacity. Engineered exosomes have been explored as delivery vehicles for siRNAs, CRISPR-Cas9 components, and chemotherapeutic agents, thereby addressing drug solubility, targeting specificity, and systemic toxicity. Furthermore, their endogenous immunomodulatory and regenerative functions position them as candidates for applications in inflammatory, neurodegenerative, and autoimmune disorders (*Mori et al., 2023; Kalluri et al., 2020*). However, technical challenges remain. The lack of standardised protocols for exosome

isolation, characterisation, and quantification poses significant barriers to clinical translation (*Wang et al., 2024; Urbanelli et al., 2015*).

Nevertheless, ongoing advances in microfluidics, nanotechnology, and bioinformatics continue to refine the field of exosomal proteomics. These innovations promise to enhance analytical sensitivity, improve scalability, and standardise downstream applications, thereby facilitating the incorporation of exosome-based strategies into the clinical arsenal of personalised medicine (*Debbarma et al., 2024*). As research progresses, exosomal proteomics holds the potential to revolutionise precision healthcare by enabling real-time, minimally invasive insights into patient-specific disease biology and response to treatment.

1.1 Exosomes as Highly Specific Biomarkers

Exosomes are nanoscale extracellular vesicles, typically 30-150 nm in diameter, that are secreted by nearly all cell types and found in a variety of biofluids. Their widespread presence in fluids such as blood, saliva, and urine, combined with a protective lipid bilayer, makes them exceptionally stable and ideal candidates for non-invasive diagnostics (Zhou, 2024; *Kim et al., 2018; Boriachek et al., 2018).* This bilayer encloses a diverse array of bioactive molecules, including proteins, lipids, RNA, and DNA, which reflect the physiological or pathological status of their originating cells. These vesicles mediate intercellular communication by transferring functional biomolecules that influence critical processes such as tumour proliferation, immune modulation, and tissue homeostasis (Zhou, 2024*; Boriachek et al., 2018*). Their content mirrors the molecular state of the parent cell, allowing them to function as liquid biopsies, particularly in oncology and cardiovascular diagnostics, where they provide insight into disease onset, progression, and therapeutic response (*Lin et al., 2020*; Kalluri, 2016).

Advanced analytical tools, including ultracentrifugation and microfluidics, have enhanced the ability to isolate and characterise exosomes with high specificity. Despite this, challenges remain in the standardisation of isolation protocols, limiting reproducibility across studies (*Hochendoner et al., 2018; Boriachek et al., 2018*). In neurological applications, exosomes are increasingly employed due to their capacity to traverse the blood-brain barrier, enabling precise delivery of therapeutic payloads (*Kudpage et al., 2024*). Importantly, exosomes demonstrate remarkable potential in cancer diagnostics due to their enrichment in tumour-specific proteins, RNAs, and DNAs. This molecular cargo enables early detection, real-time monitoring of disease progression, and response to therapy (*Gao et al., 2018*; *Yu et al., 2023*). Their stability and resistance to enzymatic degradation provide a distinct advantage over other biomarkers found in plasma or serum (*Jin et al., 2024; Jiang et al., 2019; Roychowdhury, 2024).*

In cancer biology, exosomes are implicated in processes such as tumour growth, survival, and metastatic spread. Their inhibition is being explored as a therapeutic strategy, and their biocompatibility makes them suitable as drug delivery vehicles (*Nafar et al., 2022*; *Ebrahimi et al., 2024; Rani et al., 2020*). Cardiovascular studies have also identified exosomal miRNAs as indicators of myocardial infarction and atherosclerosis (*Li et al., 2018; Ndoni et al., 2022*), further affirming their utility in non-invasive diagnostics. The engineered use of exosomes to transport chemotherapeutic agents directly to tumour sites has shown potential to minimise systemic toxicity and improve treatment efficacy (*Jiang et al., 2019; Mohseni et al., 2025*). Their immunomodulatory functions and ability to condition pre-metastatic niches emphasise their dual role in diagnostics and therapeutics (*Aghebati-Maleki et al., 2019;* Munson & Shukla, 2015).

Despite these advancements, issues such as large-scale production, cargo heterogeneity, and regulatory limitations remain barriers to their clinical translation (*Mosquera-Heredia et al., 2021*; *Dwivedi et al., 2023*). Nevertheless, exosomes represent a transformative platform for precision medicine by offering patient-specific diagnostic and therapeutic options that are minimally invasive and biologically compatible (Alshubaily &

Al-Zahrani, 2021). In diseases such as non-small cell lung carcinoma, exosomes facilitate early-stage detection via stable tumour-derived antigens (*Yang et al., 2023)*. Their encapsulated microRNAs (miRNAs) have emerged as robust diagnostic and prognostic biomarkers, and their stability within exosomes enhances their diagnostic longevity (*Preethi et al., 2022*).

Exosome-based proteomic profiling holds significant promise for enhancing personalised medicine, particularly in the context of chronic diseases including diabetes, neurodegenerative disorders, and cardiovascular disease (*Debbarma et al., 2024*; Al-Madhagi, 2024; Kang, 2019). Their capacity to cross biological barriers such as the blood-brain barrier and carry CRISPR/Cas systems or RNA therapeutics adds to their therapeutic utility (*Simpson et al., 2009; Ebrahimi et al., 2024; Urbanelli et al., 2015)*.Although standardisation and quality control remain ongoing challenges, continuous innovations in exosome proteomics are enabling deeper insights into disease mechanisms and supporting the development of individualised therapeutic strategies (*Dwivedi et al., 2023).*

2. The Exosome "Omics" Probing and Profiling: Exosomal Proteomics

2.1 Advanced Isolation Techniques Supporting Clinical Applications

The clinical integration of exosome profiling in personalised medicine necessitates the utilisation of robust isolation and characterisation methodologies, given the significance of exosomes as diagnostic and therapeutic agents. These extracellular vesicles (EVs) are found in a wide range of biological fluids, including blood, urine, and cerebrospinal fluid, making their precise isolation fundamental to any downstream clinical application. Conventional techniques such as ultracentrifugation, ultrafiltration, and polymer-based precipitation remain widely employed. Ultracentrifugation enables the isolation of exosomes of smaller diameters with reduced protein contamination, though it is labor-intensive, time-consuming, and requires specialised equipment (Ansari *et al.*, 2023). In contrast, precipitation methods offer simplicity and affordability, albeit often at the expense of purity and reproducibility (Ansari *et al.*, 2023).

Emergent microfluidic technologies present an attractive alternative, delivering high-purity isolations with significantly reduced processing time, thereby aligning with the practical needs of point-of-care diagnostics (*Contreras-Naranjo* et al*., 2017)*. Likewise, magnetic bead-based protocols allow for the high-specificity retrieval of exosomes, though they suffer from challenges concerning scalability and standardisation (*Jiawei* et al*., 2022*). The decision to employ a specific isolation method hinge on clinical priorities, including yield, purity, cost, reproducibility, and processing time (Yakubovich, 2022; Kurian *et al.*, 2021). The pivotal role of exosomes in cell-cell communication, as well as their utility as biomarkers in non-invasive diagnostics such as liquid biopsies, particularly in oncology, reinforces the demand for refined isolation technologies (*Yu* et al*., 2022*). Future advancements should priorities the standardisation and cost-effectiveness of these techniques to facilitate the seamless adoption of exosomal proteomics into personalised clinical workflows (*Gurunathan* et al*., 2019;* Sharma, 2017).

Among these methodologies, size exclusion chromatography (SEC) has emerged as a prominent and reproducible approach due to its capacity to isolate vesicles based on molecular size without the use of binding ligands. This preserves the structural and functional integrity of exosomes (Hall, 2018; Size Exclusion Chromatography (SEC), 2022). SEC demonstrates high purity in isolating key exosomal markers such as CD9, CD63, and CD81, and is both scalable and cost-efficient, making it an accessible method for laboratories with limited resources (Sidhom *et al.*, 2020; Different Isolation Techniques, 2022).Nevertheless, SEC is constrained by limitations such as low throughput owing to restricted sample load volumes and flow rates, making it less suitable for large-scale applications (Hall, 2018). It remains well-suited for exploratory research, including proteomic analyses from *Drosophila* cell lines (Pandey & Chawla, 2022). Its gentle size-dependent exclusion mechanism

permits efficient separation of proteins and nanoparticles, thereby maintaining vesicle viability for downstream analyses (Size Exclusion Chromatography (SEC), 2022). While other methods, such as immunoaffinity capture and ultracentrifugation, remain relevant, SEC's balance of efficiency and functional preservation underpins its expanding application in diagnostic and therapeutic exosome research (Sidhom *et al.*, 2020; Dissanayake *et al.*, 2021).

Immunoaffinity-based isolation leverages antibody binding to surface antigens most commonly CD63, CD9, and CD81 to selectively enrich exosome subtypes from complex biofluids. This approach often employs magnetic bead conjugates to improve yield and specificity. Oksvold *et al.* (2015) demonstrated the efficacy of this workflow using flow cytometry and electron microscopy. Further, *Jiawei* et al. *(2022)* confirmed the high purity achieved via magnetic bead-based protocols, although they highlighted high operational costs and challenges in methodological standardisation. The specificity of immunoaffinity isolation is further exemplified by Shrivastava *et al.*, who utilised cost-effective chicken-derived antibodies to capture targeted exosome populations (*Shrivastava* et al*., 2023*). Nonetheless, this method faces limitations when isolating rare or tissue-specific exosomes, such as neuronal subtypes, which require alternative markers like L1CAM or GluR2/3 for optimal capture (*Yousif* et al*., 2021*). Novel approaches using gold nanoparticles conjugated to anti-CD63 antibodies have also been explored to improve efficiency and cost-effectiveness in exosome separation from complex fluids (Efficient Strategy, 2023; Panwar *et al.*, 2023). Despite its strengths in specificity and selectivity, immunoaffinity capture remains limited by high costs and the need for refinement in targeting less abundant exosome populations.

Microfluidic-based isolation platforms have recently revolutionised the field by enabling rapid, sensitive, and highly specific separation of exosomes based on physical and biochemical attributes. These miniaturised systems offer enhanced recovery rates, reduced sample volumes, and integrated analytical capabilities (Kumar *et al.*, 2023). Gao *et al.* (2023) and Ding *et al.* (2021) noted that such lab-on-a-chip devices improve yield and purity while shortening isolation times, making them particularly suited for real-time diagnostic applications. Integration of microfluidic technology with traditional approaches, such as immunomagnetic bead capture, has led to hybrid systems capable of continuous and automated workflows (Niu *et al.*, 2020). These advances are crucial for clinical settings, enabling in situ exosome characterisation for early cancer detection, prognosis, and personalised treatment (Xu & Ye, 2023).

However, translational barriers persist, including the high cost of chip fabrication and the need for enhanced reproducibility across diverse biological matrices (*Kumar* et al*., 2023; Chen* et al*., 2022).* Nonetheless, the potential of microfluidic platforms to reshape exosome analysis remains considerable, with research focusing on their further miniaturisation, multiplexing capabilities, and integration into point-of-care diagnostic platforms (*Raju* et al*., 2022; Wang* et al*., 2023*). In summary, each sophisticated isolation strategy contributes uniquely to the yield, specificity, and integrity of exosomes derived from various biological matrices. Optimal method selection must be dictated by clinical and analytical demands, factoring in efficiency, scalability, reproducibility, and cost. The evolution of these technologies will underpin the successful deployment of exosomal proteomics in precision diagnostics and therapeutics.

2.2 Scale of Proteins through Mass Spectrometry and Quantitative Analysis

Mass spectrometry (MS) based proteomic analysis of exosomes has become a cornerstone in elucidating the molecular underpinnings of diverse pathological conditions and in identifying viable therapeutic targets. Exosomes, a subset of small EVs, are instrumental in mediating intercellular communication by transporting proteins, lipids, and nucleic acids. Proteomic interrogation of these vesicles is especially critical in oncology, where exosomes mirror the altered proteomic landscape of their parental tumour cells, thereby contributing to key processes such

as tumour invasion and metastasis (*Wang et al.*, 2020; *Simona et al.*, 2013).

Recent technological advancements in MS have markedly increased the sensitivity, dynamic range, and resolution of proteomic workflows, enabling the detection of low-abundance proteins within exosomes (*Xu et al.*, 2020; *Angel et al.*, 2012). When integrated with refined bioinformatics tools and expansive proteome databases, these enhancements have allowed for comprehensive profiling of exosomal proteomes, thereby uncovering insights into their biological roles and clinical potential as biomarkers (*Jin et al.*, n.d.). For instance, MS-based analyses have catalogued protein compositions of tumour-derived exosomes in prostate and bladder cancers, highlighting their biomarker utility (*Wang et al.*, 2020). Furthermore, the fusion of MS with advanced separation technologies such as ion mobility spectrometry and lab-on-a-chip microfluidic systems has refined proteome resolution and deepened the biological interpretability of exosomal content (*Angel et al.*, 2012). These methodological innovations underpin the application of exosomal proteomics in precision medicine, supporting both diagnostic monitoring and the stratification of personalised therapeutic interventions (*Olver and Vidal*, 2007; *Simpson et al.*, 2009).

In terms of quantification strategies, label-free quantification (LFQ) and isotopic labelling represent two dominant approaches, each with specific methodological benefits and constraints. LFQ estimates protein abundance by comparing peptide ion intensities, providing broad proteome coverage and high throughput, albeit with sensitivity to ionisation efficiency variability and necessitating rigorous data normalisation (*Wang et al.*, 2006; *Ankney et al.*, 2018). Conversely, stable isotope labelling methods including metabolic labelling and ^18O-labelling introduce known mass differentials to accurately compare experimental conditions and are particularly suited for quantifying post-translational modifications (PTMs) such as phosphorylation and glycosylation, which are vital for deciphering disease pathophysiology (*Yuan et al.*, 2009; *Anand et al.*, 2017; *Liu et al.*, 2020).

Despite their strengths, isotope labelling techniques can be cost-prohibitive and operationally demanding, requiring sophisticated instrumentation and expert handling (*Virág et al.*, 2024). Nonetheless, the combined use of LFQ and isotope-based methodologies significantly advances exosomal proteomic studies, contributing to the identification of disease-associated signatures and the development of personalised diagnostic tools (*Chia et al.*, 2017; *Yao et al.*, 2013).MS remains a pivotal analytical modality in capturing protein dynamics and PTMs essential for understanding molecular disease mechanisms (*Hoshino*, 2015; *Pan et al.*, 2009). However, the complexity and multi-step nature of MS workflows, alongside the lack of universally adopted standards, continue to impede cross-study reproducibility (*Yao et al.*, 2013). Addressing these methodological variabilities will be vital for integrating exosomal proteomics into clinical diagnostics and personalised therapeutics (*Chia et al.*, 2017; *Liu et al.*, 2020).

2.3 Reproducibility and Standardisation Challenges

Achieving reproducibility and standardisation in exosomal proteomics remains a persistent obstacle due to the variability in exosome isolation techniques, sample handling protocols, and lab-specific analytical procedures. The International Society for Extracellular Vesicles (ISEV) has taken a proactive stance in remedying this through the MISEV2018 guidelines, which promote inter-laboratory consistency and methodological transparency (*Nieuwland et al.*, 2020; *Yadav et al.*, 2024). These guidelines underscore the importance of harmonised protocols for sample acquisition, processing, and data analysis as foundational requirements for reproducible outcomes in both research and clinical applications (*Nieuwland et al.*, 2020).

Nevertheless, challenges persist, notably the heterogeneity of vesicle populations and the multifaceted nature of EV isolation, which together compromise reproducibility and translational feasibility (*Yadav et al.*, 2024; *Jablonska et al.*, 2019). Common isolation methods such as ultracentrifugation, polymer-based

precipitation, and immunoaffinity capture each present trade-offs in terms of yield, purity, and operational complexity (*Zhou et al.*, 2020; *Abramowicz et al.*, 2016). The absence of universally recognised Good Manufacturing Practices (GMP) and standard reference materials further exacerbates inconsistencies across studies (*Lai et al.*, 2022). Platforms such as EV-TRACK and repositories like EVpedia and ExoCarta, have been instrumental in fostering open data practices and promoting standardisation efforts within the *extracellular vesicle* research community (*Yadav et al.*, 2024). Additionally, innovations in isolation technologies, including size-exclusion chromatography (SEC) and MS-compatible purification workflows, are contributing to higher fidelity in exosome preparations for downstream proteomic analyses (*Abramowicz et al.*, 2016; *Abramowicz et al.*, 2018).

Parallel to methodological advances, efforts are ongoing to establish globally accepted reference materials and internal controls that could serve as benchmarking tools across laboratories. These materials are indispensable for reducing inter-laboratory variability and for ensuring robust, quantifiable outputs in exosome-based proteomics. Adoption of universally accepted reproducibility metrics and workflow validation protocols will be pivotal in overcoming current translational barriers and facilitating the clinical implementation of personalised exosome-based diagnostics. Optimising personalised medicine through exosomal proteomics necessitates rigorous approaches to exosome isolation, characterisation, and quantitative protein profiling. Techniques such as SEC, immunoaffinity capture, and microfluidic enrichment facilitate the acquisition of high-purity vesicle populations, which is critical for accurate biomarker detection. Advanced proteomic workflows, leveraging MS technologies, enable comprehensive profiling of exosomal proteins, including rare and modified species. To fully realise the diagnostic and therapeutic promise of exosomes, reproducibility standards must be stringently enforced across the proteomic pipeline. Addressing these challenges will empower the deployment of exosome-based solutions in precision medicine, enabling patient stratification, targeted therapy, and real-time disease monitoring with enhanced clinical utility.

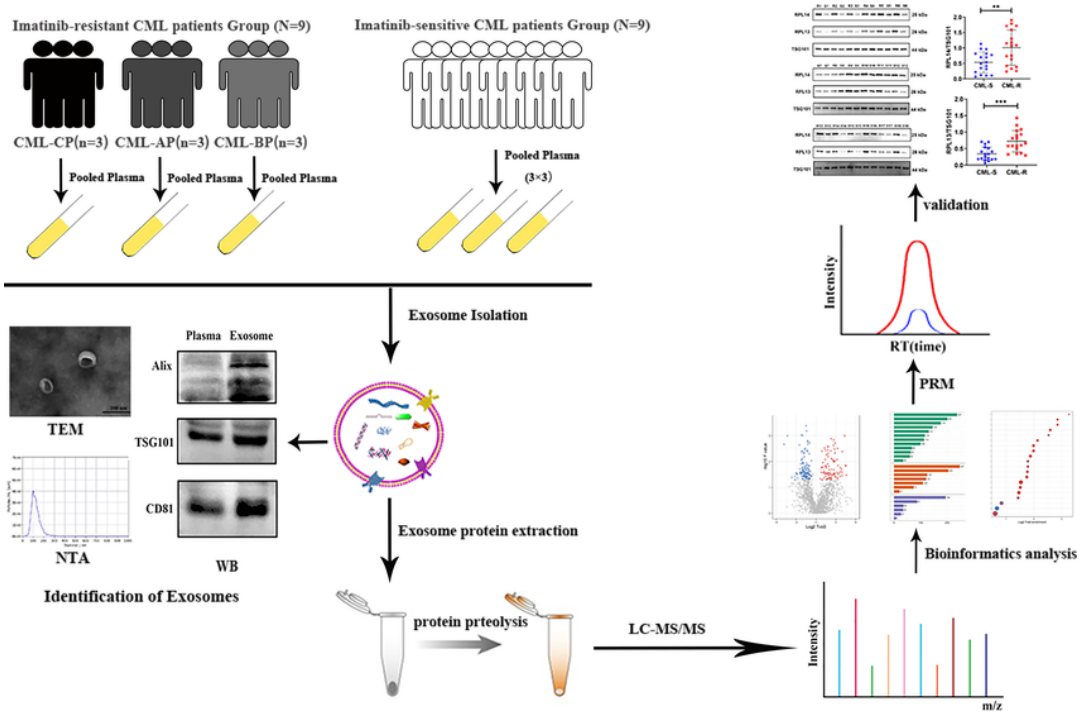

Figure 1: Integrated Workflow for Exosomal Proteomics Using Mass Spectrometry (Adapted from Li, M-Y., Zhao, C., Chen, L., Yao, F-Y., Zhong, F., Chen, Y., Xu, S., Jiang, J-Y., Yang, Y-L., Min, Q-H., Lin, J., Zhang, H-B., Liu, J., Wang, X-Z. & Huang, B. (2021) .

This schematic workflow shows the LC-MS/MS-based quantitative proteomic analysis of exosomes isolated from plasma samples of IM-R and IM-S CML patients. CML, chronic myeloid leukemia; CP, chronic phase; BP, blastic phase; AP, acceleration phase; TEM, transmission electron microscope; NTA, nanoparticle tracking analysis; WB, western blot; LC-MS/MS, liquid chromatography-tandem mass spectrometry.

3. Disease-Specific Exosomal Proteomic Signatures for Personalised Treatments

3.1 Exosomal Proteomes Unique in Cancer

Exosomal proteomes offer a non-invasive window into tumour biology, conveying biomarkers that inform tumour complexity, treatment response, and prognosis. Tumour cells shed exosomes into the bloodstream and other bodily fluids, with their proteomic cargo reflecting the cellular and microenvironmental alterations associated with malignancy. Analysing these protein signatures can reveal mechanisms of tumour progression, treatment resistance, and heterogeneity, facilitating tailored therapeutic interventions.

Tumour heterogeneity, characterised by the coexistence of diverse sub clonal populations, poses significant clinical challenges. Traditional imaging modalities such as ultrasound and MRI provide structural data but lack molecular specificity. By contrast, exosomal content offers a dynamic readout of tumour heterogeneity, for example, elevated exosomal human epidermal growth factor receptor 2 (HER2) has shown promise as a real-time biomarker to guide therapy in HER2-positive breast cancer. Exosomal HER2 correlates with disease aggressiveness and may indicate emerging resistance to therapies such as trastuzumab (*Moon et al*., 2024; *Jiang et al*., 2024). Research reveals that circulating exosomal miRNAs, including miR-1246 and miR-155, are predictive of trastuzumab resistance, highlighting the diagnostic value of exosome-derived nucleic acids (*Zhang et al*., 2020; *Zuo et al*., 2021).

In colorectal cancer (CRC), carcinoembryonic antigen (CEA) is an established biomarker used in clinical practice. Recent evidence indicates that exosomal CEA surpasses serum markers in sensitivity and may provide more reliable monitoring of therapeutic efficacy. Exosomal CEA levels dynamically reflect treatment responses to chemotherapy and immunotherapy in CRC, demonstrating stronger prognostic utility when combined with markers such as CD147 (*Campo-da-Paz et al*., 2018; *Gu et al*., 2023). Exosomal profiling, when integrated with conventional biomarkers, offers a robust tool for monitoring disease progression and management. Overall, tumour-derived exosomal proteomes provide real-time insights into tumour status, heterogeneity, and therapy response. Characterising these proteins enables clinicians to devise targeted treatment regimens that are both effective and minimally toxic, aligning with the principles of precision oncology.

3.2 Neurological Diseases and Exosomal Markers

Exosomal proteomics has gained significant traction as a minimally invasive diagnostic and mechanistic tool in neurodegenerative diseases, notably Alzheimer's disease (AD) and Parkinson's disease (PD), due in part to the capacity of exosomes to bypass the blood-brain barrier (BBB). These nanoscale vesicles can transport molecular cargo proteins, lipids, and nucleic acids from the central nervous system (CNS) into peripheral fluids such as blood and saliva, providing a "window" into brain pathology (*Rani et al*., 2020; *Younas et al*., 2022). In AD, exosomes carry pathological hallmarks, including amyloid-β and hyperphosphorylated tau (*pTau*, notably at Thr181 and Ser396), which are implicated in neurofibrillary tangle formation. Numerous studies have demonstrated that levels of pTau and amyloid-β in exosomes are significantly elevated in patients compared to controls, underscoring their potential as early diagnostic biomarkers (*Saman et al*., 2012; *Sun et al*., 2020; *Cai et al*., 2022). Meta-analyses confirm that brain-derived exosomal amyloid-β42 (SMD 1.53, $p < 0.05$) and p-Tau-181 (SMD 4.04, $p < 0.001$) reliably discriminate AD from healthy individuals.

Similarly, in PD, exosomal α-synuclein levels derived from neuronal sources are markedly elevated. Early reports found plasma exosomal α-

synuclein to be higher in PD than in controls, with moderate diagnostic accuracy (AUC≈0.65). Further validation across multiple cohorts, including prodromal PD, identified a ~2-fold increase in neuronal exosomal α-synuclein, independent of disease severity, suggesting its use as a pharmacodynamic biomarker (*turn0search1*). Meta-analytic assessments corroborate its significant elevation (SMD ~1.37, $p < 0.001$) in both total and neuron-derived exosomes. Advanced detection techniques, including immunocapture using L1CAM and protein misfolding cyclic amplification, have further improved the specificity and sensitivity of α-synuclein detection.

Beyond diagnostic utility, exosomal cargoes are increasingly recognised as mediators of disease pathophysiology and potential therapeutic targets. For instance, exosome-mediated propagation of amyloid-β, tau, and misfolded α-synuclein may contribute to the progressive spread of neurodegenerative pathology in AD and PD (*Alzahrani et al.*, 2024; *Rastogi et al.*, 2021; *Shi et al.*, 2023). Moreover, exosomes themselves are being investigated as drug-delivery vehicles to the CNS, offering novel therapeutic modalities (*Kudpage et al.*, 2024). However, technical challenges persist, particularly regarding the standardisation of exosome isolation and the heterogeneity inherent to CNS-derived vesicles (*Younas et al.*, 2022; *Kudpage et al.*, 2024). Developing robust, validated protocols remains critical for translating exosomal biomarkers into clinical practice.In summary, exosomal proteomics has emerged as a transformative approach in neurology, facilitating early diagnosis, tracking disease progression, and elucidating mechanisms for targeted intervention. Continued refinement of vesicle isolation techniques and quantitative methodologies will be essential to unlock their full translational potential (*Osaid et al.*, 2023; *Fan et al.*, 2022).

3.3 Infectious Disease and Autoimmune Profiles

Exosomes, nanoscale lipid bilayer-bound extracellular vesicles, serve as pivotal agents in modulating immune responses and inflammation, thereby influencing the pathophysiology of infectious and autoimmune diseases. These vesicles convey a multitude of bioactive cargos including proteins, microRNAs (miRNAs), DNA fragments, lipids, and immune modulators thereby facilitating intercellular communication between immune cells and peripheral tissues (*Hussain, Zhao and Rahman*, 2022; *Umeche and Olaniyan*, 2023). The immunomodulatory potential of exosomes stems from their ability to influence both innate and adaptive immunity, particularly under pathophysiological conditions.

3.3.1 Autoimmune Pathogenesis and Exosomal miRNAs

In autoimmune diseases, exosomes derived from immune and non-immune cells contain distinct miRNA signatures that actively participate in the dysregulation of immune tolerance. For example, in *type 1 diabetes mellitus* (T1DM), miR-142-3p, miR-142-5p, and miR-155 commonly packaged in exosomes have been shown to induce β-cell apoptosis, highlighting their role in disease initiation (*Jayaseelan and Arumugam*, 2019). Similarly, exosomes from antigen-presenting cells such as dendritic cells and B cells carry peptide-loaded major histocompatibility complex (MHC) molecules, which can directly activate autoreactive T cells (*Shenoda and Ajit*, 2016). In systemic lupus erythematosus (SLE), exosomes from patient serum are enriched with pro-inflammatory cytokines, autoantibodies, and nucleic acid fragments. These contribute to immune complex formation and type I interferon pathway activation hallmarks of lupus flares (*Chan et al.*, 2019). In *rheumatoid arthritis* (RA), synovial fluid-derived exosomes have been found to encapsulate citrullinated proteins and TNF-α, correlating with joint inflammation and radiographic damage.

Table 1. Exosome-associated Biomarkers in Autoimmune Diseases

Disease	Exosomal Cargo	Source	Pathological Role
T1DM	miR-142-3p, miR-155	T lymphocyte-derived exosomes	Induction of β-cell apoptosis
SLE	Autoantibodies, dsDNA, IFN-inducible RNAs	Circulating serum exosomes	Immune complex formation
RA	Citrullinated peptides, TNF-α	Synovial fluid exosomes	Joint inflammation & cartilage damage

Sources: Jayaseelan and Arumugam (2019); Chan et al. (2019); Shenoda and Ajit (2016)

3.3.2 Exosomes in Viral and Bacterial Infections

In the context of viral infections, exosomes serve dualistic roles: they may propagate infection by transporting viral elements, or support immunity by amplifying host defences. Exosomes secreted from *HIV*-infected cells, for instance, carry viral Nef protein, TAR-RNA, and co-receptors such as CCR5 and CXCR4, enhancing viral spread and immune escape (*Hussain, Zhao and Rahman*, 2022). Conversely, exosomes from innate immune cells can shuttle antiviral restriction factors (e.g., APOBEC3G, IFITM3), thereby suppressing viral replication.

Exosomes also play roles in *hepatitis C virus* (HCV) infection, where they serve as vehicles for HCV RNA transfer between hepatocytes, bypassing neutralising antibodies and contributing to viral persistence. Moreover, exosomes have emerged as contributors to antiviral drug resistance through the horizontal transfer of drug-resistance-associated proteins and RNAs (*Joseph, Wang and Lee*, 2021).

Table 2. Exosomal Interactions in Viral Infections

Virus	Exosomal Component	Functional Impact
HIV	Nef, TAR-RNA, CCR5, CXCR4	Immune evasion and increased infectivity
HCV	Full-length viral RNA	Antibody escape, persistence
Influenza A	M2 protein, miR-483-3p	Suppression of the IFN-β pathway

Sources: Joseph et al. (2021); Hussain, Zhao and Rahman (2022)

3.3.3 Immunotherapeutic and Diagnostic Implications

Due to their stability and molecular diversity, exosomes are now under investigation as precision diagnostic tools and therapeutic agents. In autoimmune diseases, exosomal miRNAs serve as dynamic biomarkers capable of tracking disease exacerbation or remission phases. Similarly, in infectious diseases, the profiling of pathogen-derived exosomal components may enhance early detection and treatment response monitoring. In neurodegenerative disorders such as *Alzheimer's disease*, exosomes bearing tau and β-amyloid proteins offer early diagnostic potential, while in cancer, exosomal HER2 and CEA have been incorporated into clinical workflows for prognostic evaluation. These findings reflect the growing consensus that exosomal proteomics can underpin the stratification of patient-specific therapies in precision medicine.

Clinical Implications of Exosome-based Profiling

- Real-time disease activity tracking in SLE and RA

- Early detection of HIV viral rebound during therapy
- Detection of cancer resistance mutations (e.g., KRAS, EGFR) in exosomes
- Monitoring neuroinflammation in multiple sclerosis through CSF exosomes

Exosomes play multifaceted roles in mediating immune regulation, pathogen spread, and autoimmune disruption. Their utility spans from molecular diagnostics to immunotherapeutic innovation, supported by advances in mass spectrometry and high-throughput profiling technologies. By decoding the proteomic and transcriptomic contents of exosomes, researchers and clinicians can not only identify disease-specific signatures but also tailor therapeutic interventions. Thus, exosomal proteomics emerges as a frontier for biomarker discovery, personalised medicine, and disease surveillance.

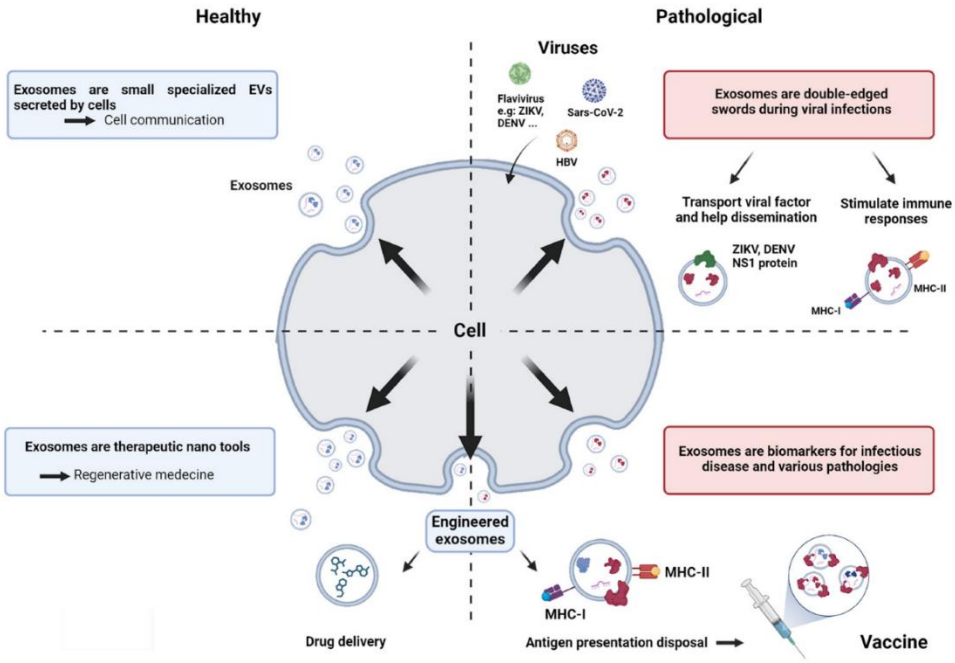

Figure 2: Mechanisms of Exosome-Mediated Immune Modulation in Autoimmune and Infectious Diseases. Adapted from El Safadi, D., Mokhtari, A., Krejbich, M., Lagrave, A., Hirigoyen, U., Lebeau, G., Viranaicken, W., & Krejbich-Trotot, P. (2024). "Exosomes are double-edged swords during infection…"

This schematic elegantly illustrates the dualistic immunomodulatory roles of exosomes in health and disease. On one hand, pathogen-derived or infected-cell exosomes act as immune evasion tools, transporting viral proteins, pathogen-associated molecular patterns (PAMPs), or inhibitory miRNAs to recipient cells to facilitate viral persistence and immunosuppression. On the other hand, exosomes derived from immune cells or stem cells can enhance innate immunity, delivering antiviral miRNAs, cytokines, or antigenic peptides capable of stimulating dendritic cells, T cells, and natural killer (NK) cells. The same figure encompasses exosomal functions in autoimmune contexts, such as antigen presentation (e.g., MHC-peptide complexes) and pro-inflammatory cargo, which exacerbate tissue pathology in diseases like SLE and RA. At its core, the schematic illustrates how exosomal proteomic content informs immune modulation, targeting and stratifying patients across infectious, autoimmune, neurodegenerative, and oncological conditions, thus representing a central tool in precision medicine.

4. Role of Exosomal Proteomics in Monitoring Drug Resistance and Assessing Response Prediction

4.1 Detection of Diagnostic and Predictive Biomarkers

The proteomic profiling of exosomes has emerged as a vital approach for predictive modelling in oncology, particularly in the personalisation of cancer therapies. Exosomal proteins reflective of the molecular state of originating tumour cells can serve as non-invasive indicators of drug sensitivity, thereby enhancing therapeutic stratification and outcome prediction. This modality permits the continuous monitoring of disease dynamics and treatment efficacy through a liquid biopsy framework, offering a real-time view of tumour evolution and drug response (Kalluri and LeBleu, 2020).

In *non-small cell lung cancer* (NSCLC), the analysis of exosomal proteins has proven particularly valuable in evaluating response to *epidermal growth factor receptor* (EGFR)-targeted therapies. The presence of mutant EGFR in exosomes isolated from plasma samples provides insight into potential responsiveness to tyrosine kinase inhibitors (TKIs). Notably, *Sandfeld-Paulsen* et al. (2016) demonstrated that elevated levels of exosomal EGFR and specific mutation signatures were predictive of favourable outcomes with EGFR-TKI treatment. These findings underline the potential of blood-derived exosomes as surrogate biomarkers for guiding therapeutic decisions, enabling clinicians to forecast treatment efficacy and pre-emptively adjust strategies based on molecular cues.

Beyond EGFR, tumour-derived exosomes encapsulate a myriad of signalling molecules and protein fragments that reflect the tumour's adaptive landscape. For example, the detection of exosomal markers associated with *tumour necrosis factor-alpha* (TNF-α) signalling pathways suggests a mechanistic link to metastasis and treatment resistance. Such insights inform clinicians of actionable molecular targets, aiding in the early identification of resistance mechanisms and facilitating intervention before metastatic dissemination (*Xu* et al., *2020*). Furthermore, the clinical utility of exosomal proteomics extends beyond oncology. In neurodegenerative disorders, autoimmune conditions, and viral infections, exosomal protein signatures offer a window into pathological processes that are otherwise difficult to monitor. The differential expression of disease-specific exosomal proteins facilitates early diagnosis, tracks therapeutic impact, and supports personalised care planning (Witwer and Théry, 2019; *Yanez-Mo* et al., *2015*).

In summary, the ability to decode the exosomal proteome equips physicians with molecular-level insight, allowing for precise and adaptive treatment strategies. This enhances not only diagnostic accuracy but also therapeutic specificity, accelerating the integration of exosome-based biomarkers into precision medicine frameworks.

4.2 Monitoring Resistance Mechanisms

The emergence of therapeutic resistance remains a formidable obstacle in the management of cancer and other complex diseases. Recent advances in exosomal proteomics have enabled dynamic, real-time monitoring of resistance pathways, thereby offering insights into cellular adaptation processes under therapeutic pressure. Exosomes, as nanoscale extracellular vesicles, function not only as messengers of intercellular communication but also as vectors of drug resistance, reflecting phenotypic and proteomic shifts occurring in tumour cells during exposure to chemotherapy, targeted agents, or immunotherapies. Of particular interest is *exosome*-mediated chemoresistance, a rapidly advancing domain in oncological research. These vesicles are known to encapsulate and transfer drug efflux transporters such as P-glycoprotein (P-gp), thereby facilitating the active removal of chemotherapeutic agents from intracellular compartments. This mechanism significantly undermines drug efficacy and contributes to treatment failure. *Chen et al.* (2018) demonstrated that exosomes isolated from drug-resistant breast and ovarian cancer cells exhibit enriched levels of P-gp and other resistance-

associated proteins, facilitating the horizontal transfer of resistance phenotypes within tumour populations.

Quantitative proteomic profiling of exosomes collected longitudinally from patients undergoing chemotherapy allows for the early detection of resistance biomarkers, including ATP-binding cassette (ABC) transporters such as P-gp and ABCG2. Monitoring such signatures can provide actionable insights into evolving resistance, enabling clinicians to modify therapeutic regimens before clinical resistance manifests fully (*Chen et al*., 2018; *Kalluri and LeBleu*, 2020).Beyond drug efflux mechanisms, exosomes also carry a diverse array of pro-survival molecules, including epithelial-mesenchymal transition (EMT)-related transcription factors, DNA repair enzymes, and anti-apoptotic proteins, which collectively promote tumour cell resilience under therapeutic duress (*Kowal et al*., 2016). The exosomal proteome thus serves as a responsive indicator of tumour plasticity, capturing the dynamic shifts in oncogenic signalling and molecular defence strategies. Early identification of such proteomic shifts facilitates pre-emptive intervention and the potential circumvention of full-scale therapeutic resistance.

Furthermore, stromal components of the tumour microenvironment, such as cancer-associated fibroblasts (CAFs), are also implicated in resistance propagation through their exosomal secretions. These exosomes are enriched in cytokines, growth factors, and regulatory RNAs that modulate tumour cell survival and modulate immune evasion mechanisms (*Whiteside*, 2016). By fostering an environment that supports immune suppression, enhanced drug clearance, and continued tumour proliferation, stromal-derived exosomes augment the complexity of therapeutic resistance. A comprehensive exosomal analysis encompassing both tumour-derived and stromal-origin exosomes can yield a more nuanced understanding of the multilayered resistance landscape. Such integrative profiling enhances the capacity to detect incipient resistance, allowing for timely adjustments to therapeutic strategies and fostering precision medicine approaches in oncology.

4.3 Modification of Treatment in Real-Time

The advancement of exosomal proteomics has introduced a transformative paradigm in therapeutic monitoring, particularly in enabling real-time assessment of treatment efficacy. Conventional protocols often rely on imaging or tissue biopsy, methods that are typically invasive, temporally delayed, and may not reflect the tumour's dynamic molecular state. In contrast, exosome-derived liquid biopsies offer a noninvasive, repeatable, and temporally responsive alternative that facilitates the timely evaluation of treatment response (*Yu* et al*., 2017; Oeyen* et al*., 2020*).

Dynamic profiling of exosomal proteomes enables the monitoring of proteomic fluctuations throughout the treatment course, yielding actionable insights into tumour adaptation, the emergence of drug resistance, and molecular remodelling. For instance, the study by Yu *et al.* (2017) demonstrated that serial analysis of exosomal epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) expression provided critical insights into shifting tumour phenotypes and therapeutic responsiveness. Such real-time molecular surveillance permits timely intervention—whether through dose adjustment, therapy switching, or combination regimens based on evolving proteomic data.

In the context of immunotherapy and molecularly targeted agents, exosomal proteomics can serve as a functional readout of the immune milieu and target engagement. Exosomal markers of immune activation, cytokine dynamics, or immune checkpoint modulation offer surrogate indicators of therapeutic efficacy and immune reactivity (Liu *et al*., 2021). Similarly, in targeted therapy, exosome analysis may detect changes in protein expression or the emergence of mutations conferring resistance, thereby informing the need for alternative treatment strategies (Zhang *et al*., 2019).

Moreover, exosome-based liquid biopsies are uniquely advantageous for monitoring tumours situated in anatomically inaccessible regions or in

patients for whom repeated tissue biopsies are contraindicated. These minimally invasive assays enable frequent sampling, offering a near-continuous molecular narrative of tumour evolution. Exosomal proteomic profiling thus provides clinicians with real-time data that guide therapeutic decision-making based on current oncogenic and resistance landscapes (Royo *et al.*, 2023). The prognostic and predictive potential of exosomal biomarkers also extends to anticipating therapeutic response and delineating resistance pathways. Exosomal proteins indicative of multidrug resistance mechanisms, such as ATP-binding cassette (ABC) transporters, stress-response chaperones, and microenvironmental modulators, can be detected before overt clinical progression, enabling pre-emptive therapeutic modifications (Whiteside, 2018; Lee *et al.*, 2022).

As exosomal profiling continues to evolve, it offers a real-time, personalised approach to oncology treatment. By integrating exosomal data into clinical workflows, oncologists can implement adaptive therapy strategies aligned with the patient's dynamic molecular status. This paradigm fosters more responsive, targeted, and effective treatment regimens, ultimately contributing to improved outcomes and minimised toxicity.

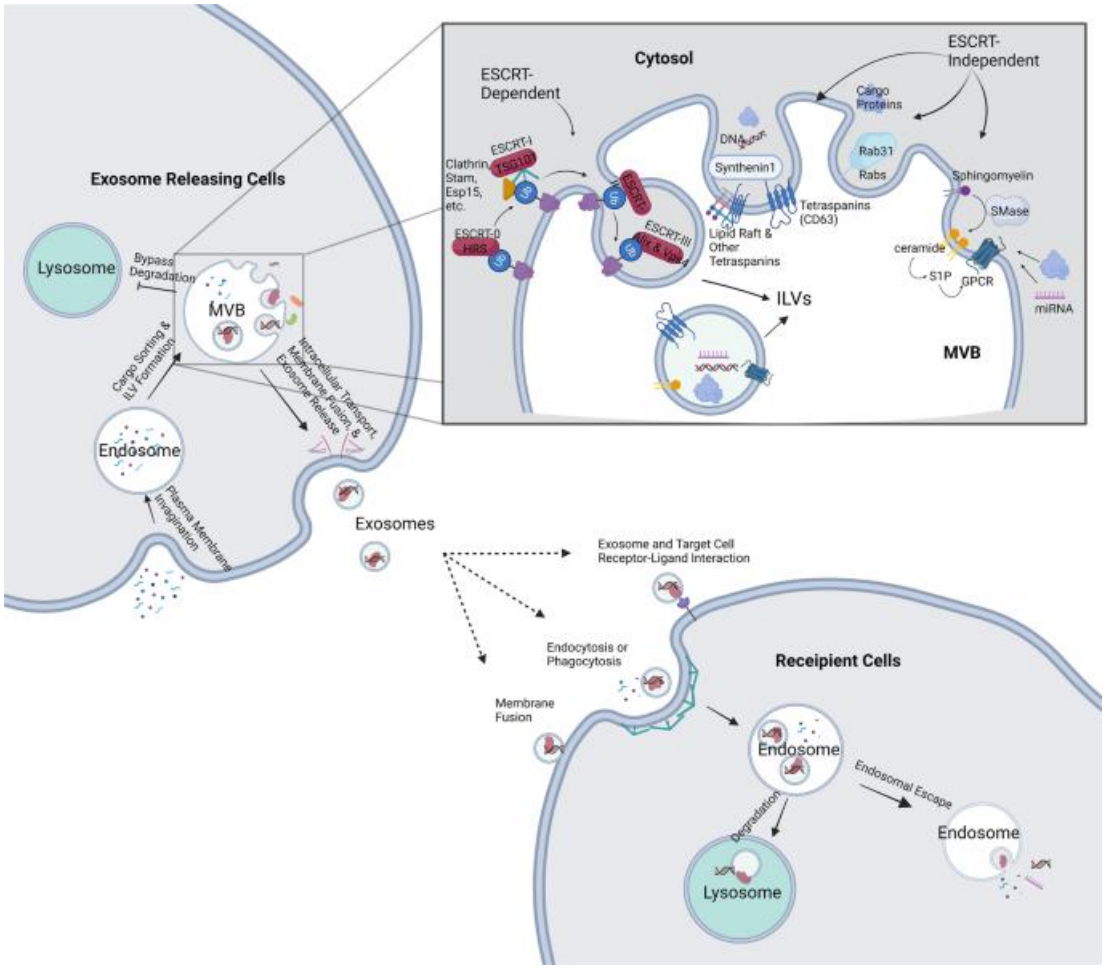

Figure 3: Mass Spectrometry-Enabled Exosomal Profiling for Adaptive Oncology Therapy. (Source: Wang, X., Tian, L., Lu, J. *et al.* Exosomes and cancer - Diagnostic and prognostic biomarkers and therapeutic vehicle. *Oncogenesis* 11, 54 (2022).

This diagram illustrates a comprehensive workflow for dynamic, proteomics-based oncology treatment monitoring. It begins with patient sample collection (such as blood or urine), followed by exosome isolation using techniques like size-exclusion chromatography or immunoaffinity capture. The isolated vesicles undergo protein extraction and digestion, preparing them for mass spectrometry (MS) analysis, where techniques such as LC-MS/MS quantify proteome changes. The data is visualised on a bioinformatics dashboard, highlighting significant protein alterations, such as increased expression of EGFR, HER2, or markers of therapy resistance. A clinical decision-making wheel then integrates these findings, guiding routines such as dose escalation, therapy switching, or combination regimens. This figure emphasises *real-time adaptive oncology*, where exosomal proteomics informs immediate, patient-specific therapeutic adjustments.

5. Developing and Exploiting Exosomes for Custom Therapeutic Delivery Systems

Exosomes are nanoscale vesicles endogenously produced by cells to facilitate the intercellular transfer of biomolecules, including proteins, lipids, and nucleic acids. Their intrinsic biocompatibility, low immunogenicity, and capacity to traverse biological barriers render them uniquely suited for application as therapeutic delivery vectors (Kalluri and LeBleu, 2020). Beyond their established role in diagnostics, exosomes are being increasingly engineered to function as bespoke drug delivery systems capable of targeting pathological tissues with high specificity, thereby mitigating systemic toxicity and off-target effects (Elsharkasy *et al.*, 2020). Therapeutic customisation is facilitated through proteomic profiling and molecular engineering, which allow precise modulation of both exosomal cargo and membrane composition. Such interventions support the creation of personalised nanotherapeutics tailored to disease-specific molecular signatures, thereby enhancing therapeutic precision and efficacy (Armstrong and Stevens, 2019).

5.1 Exosomes as Drug Delivery Vehicles

A defining advantage of exosomes over synthetic nanocarriers is their innate ability to bypass physiological barriers such as the blood-brain barrier (BBB), a formidable obstacle in central nervous system (CNS) drug delivery. This capability has been exploited for the delivery of small interfering RNAs (siRNAs), microRNAs (miRNAs), and pharmacological agents to otherwise inaccessible tissues (Barile and Vassalli, 2017). A seminal study by *Alvarez-Erviti* et al. (2011) demonstrated the efficacy of systemically administered exosomes in delivering siRNA to the murine brain. In this work, dendritic cells were genetically modified to express Lamp2 b, an exosomal membrane protein, fused to the rabies virus glycoprotein (RVG) peptide, known for its affinity to neuronal acetylcholine receptors. These bioengineered exosomes were loaded with siRNA targeting *BACE1*, a gene implicated in the pathogenesis of Alzheimer's disease. Following systemic injection, the modified exosomes successfully traversed the BBB, resulting in significant gene silencing within cerebral tissue.

This pioneering approach underscores the potential of surface modification and proteomic tagging in transforming exosomes into precision-targeted delivery platforms. By conjugating targeting moieties, such as antibodies or homing peptides, to exosomal membranes, researchers can achieve selective uptake by pathological cells expressing complementary receptors, thereby enhancing therapeutic selectivity and reducing collateral cytotoxicity (*Ha* et al., *2016*).

Furthermore, exosomes derived from immune or stem cells retain membrane proteins and ligands that confer tissue-specific homing capabilities. These vesicles, inherently equipped with contextual biological cues, can autonomously localise to sites of inflammation or tumour growth. Leveraging these endogenous trafficking signals, researchers are now engineering exosomes capable of delivering their payloads in a spatiotemporally regulated manner, aligning with the goals of precision medicine (*Lener* et al., *2015; Kamerkar* et al., *2017*). The ongoing elucidation of such homing mechanisms and molecular targeting pathways is critical to advancing exosome-based therapeutics. Future

developments may further enhance the bioavailability, targeting fidelity, and therapeutic payload capacity of these natural nanocarriers, paving the way for their routine integration into clinical regimens for oncological, neurological, and autoimmune conditions.

5.2 Developing Therapeutic Exosome Proteomes

A critical frontier in the advancement of exosome-based therapeutics lies in the comprehensive engineering of their proteomic landscape, encompassing both surface-associated and intravesicular proteins. Therapeutic exosomes can be bioengineered to incorporate functional proteins, peptides, or signalling molecules through the genetic modification of donor cells. Techniques such as transfection or CRISPR/Cas-mediated gene editing are commonly employed to induce the expression of therapeutic agents that are subsequently packaged into exosomes during their biogenesis (El Andaloussi *et al.*, 2013).

One seminal example of this approach is provided by Kamerkar *et al.* (2017), who engineered mesenchymal stem cells (MSCs) to secrete exosomes loaded with small interfering RNA (siRNA) targeting the oncogenic *KRAS^G12D* mutation, a driver commonly implicated in pancreatic ductal adenocarcinoma. Systemic administration of these modified exosomes in murine models facilitated targeted delivery of the siRNA to malignant cells, resulting in *KRAS* suppression, marked tumour regression, and prolonged survival. Notably, these exosomes exhibited favourable biocompatibility and elicited minimal immunogenic responses, an essential consideration for clinical translation.

Beyond their therapeutic payload, engineered exosomes offer the potential for dual-functional use in *theranostics*, where diagnosis and therapy converge within a single vesicular platform. This is achievable by integrating therapeutic biomolecules with traceable reporters, such as fluorescent proteins or radiolabelled imaging agents, enabling clinicians to non-invasively track therapeutic distribution and efficacy in real-time (Lakhal & Wood, 2011). Such an approach holds promise for advancing personalised medicine through dynamic treatment monitoring and adaptive clinical decision-making.

Furthermore, the utility of exosome proteome engineering extends into immuno-oncology, regenerative medicine, and autoimmune disease modulation. In cancer immunotherapy, exosomes enriched with tumour-associated antigens or checkpoint inhibitors can prime host immune responses against neoplastic cells, enhancing anti-tumour efficacy (*Pitt* et al., *2016*). Conversely, exosomes harbouring anti-inflammatory mediators, such as interleukin-10 (IL-10) or transforming growth factor-beta (TGF-β), can attenuate hyperactive immune responses in autoimmune disorders like multiple sclerosis and rheumatoid arthritis, thereby providing targeted intervention with reduced systemic toxicity (Wang *et al.*, 2021).

The progressive refinement of exosomal proteome engineering, underpinned by advancements in molecular biology, nanotechnology, and systems immunology, continues to shape the translational trajectory of exosome-based therapeutics. Future efforts must prioritise the standardisation of engineering protocols, comprehensive safety profiling, and the development of scalable manufacturing platforms to enable the clinical adoption of these promising nanobiological tools.

5.3 Surface Receptor Manipulation for Precision Targeting

Effective therapeutic delivery of exosomes necessitates precision tissue targeting, which is largely governed by the interaction between exosomal surface proteins and receptors on target cells. The rational engineering of exosomes for personalised therapies is contingent upon these receptor-ligand dynamics. Notably, Wiklander *et al.* (2019) demonstrated how exosomal surface ligands can modulate biodistribution. Similarly, Hoshino *et al.* (2015) identified specific integrins, such as α6β4 and αvβ5, as critical determinants of organotropism, with preferential accumulation in the lungs and liver, respectively. Such proteomic "address labels" permit the deliberate redirection of exosomes to

pathological tissues, optimising their therapeutic index.

Advanced proteomic profiling facilitates the identification and manipulation of surface receptors to enhance cell-specific uptake. This may involve ligand engineering, wherein donor cells are genetically modified to express targeting moieties such as antibodies or ligands that are compatible with exosomal membrane proteins (*Alvarez-Erviti et al., 2011*). These bioengineered vesicles are further adaptable through post-isolation surface functionalisation techniques like click chemistry or lipid insertion (*Kooijmans et al., 2016; Jiang et al., 2020*), enabling broad-spectrum targeting across diverse pathological conditions. Such modifications must be tailored to the patient's specific molecular landscape. For instance, exosomal surfaces can be engineered to display ligands that selectively bind to unique receptors present on patient-specific tumour phenotypes (Tian *et al.*, 2014). This strategy enhances therapeutic precision while minimising off-target effects and systemic toxicity, encapsulating the foundational principles of personalised medicine.

These evolving strategies in exosomal surface receptor manipulation reflect a paradigm shift in targeted therapy, moving from generalised treatment modalities to precision guided interventions informed by proteomic and genomic insights.

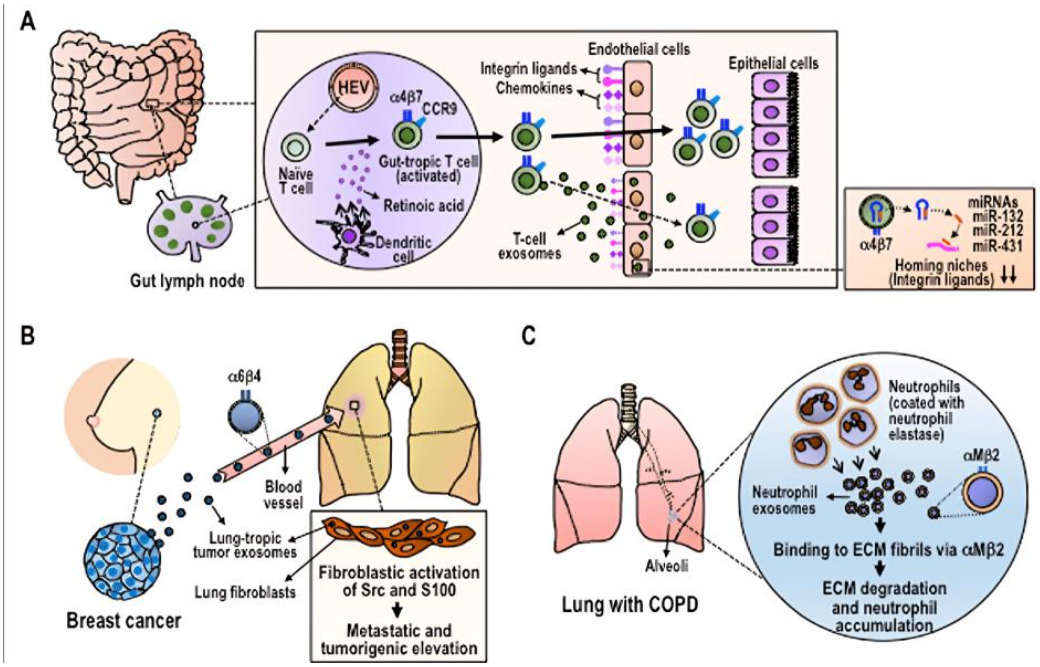

Figure 4: Integrin-Mediated Organotropism and Surface Ligand Engineering of Exosomes (Adapted from Myint, P.K., Park, E.J., Gaowa, A. *et al.* Targeted remodeling of breast cancer and immune cell homing niches by exosomal integrins. *Diagn Pathol* 15, 38 (2020).

This schematic illustrates how integrins on exosomes influence organ-specific targeting and demonstrates engineered surface modifications to enhance precision delivery. In panel (a), exosomes expressing integrin α6β4 localise to lung tissue, while those with αvβ5 preferentially accumulate in the liver, as outlined in *Hoshino et al.* (2015) and *Wiklander et al.* (2019). Panel (b) depicts strategies for surface engineering: donor cells can be genetically modified to overexpress

targeting ligands, while post-isolation techniques, such as click chemistry or lipid-anchored ligand insertion, enable direct functionalisation of purified exosomes. The visual emphasises the dual potential of proteomic "address labels" and chemical modification in guiding exosomes to specific tissues, underpinning the strategies discussed in Section 5.3.

6. Integration of Exosomes into Proteomics and Precision Medicine Frameworks

The integration of exosomal proteomics within precision medicine marks a transformative shift in the pursuit of personalised therapeutic strategies. By offering a molecular snapshot of dynamic physiological and pathological states, exosomes serve as non-invasive, real-time biosensors capable of tracking disease onset, progression, and therapeutic response. When employed within a precision medicine framework, especially in conjunction with clinical decision support systems (CDSSs) and machine learning (ML), exosomal proteomics enables stratified treatment regimens, refined therapeutic selection, and ongoing optimisation of clinical interventions. This alignment elevates precision medicine from concept to practice, anchoring it in robust molecular data.

6.1 Multi-Omics Synergy

The convergence of exosomal proteomics with other high-throughput platforms such as genomics, transcriptomics, metabolomics, and epigenomics represents a hallmark of systems biology. Each omic layer reveals distinct yet complementary aspects of cellular function: genomic data describes genetic predisposition; transcriptomic profiles reflect gene expression levels; and proteomic datasets indicate functional execution through active protein species. Exosomal proteomics adds a further spatial and temporal lens, capturing secreted peptide fragments actively participating in intercellular communication.

As demonstrated by Huang *et al.* (2020), combining exosomal proteomic and transcriptomic data in glioblastoma enabled deeper exploration into tumour heterogeneity and resistance mechanisms. Their work showed incongruity between cellular mRNA and exosomal protein expression, highlighting the vital contribution of post-transcriptional and translational modifications, phenomena only detectable through proteomic analysis.

By integrating these data streams, researchers can build comprehensive molecular signatures specific to individual patients. For example, a cancer patient exhibiting a *KRAS* gene mutation (genomics), elevated *KRAS* mRNA transcripts (transcriptomics), and overexpressed *KRAS* protein in circulating exosomes (proteomics) is an ideal candidate for anti-*KRAS* therapy. Conversely, if only the transcriptomic layer is elevated while proteomic signals are absent, this may indicate translational silencing, proteasomal degradation, or epigenetic suppression, suggesting that the therapeutic approach should be reconsidered.

Multi-omics integration thus enhances diagnostic accuracy and enables the discovery of novel therapeutic targets. In diseases such as Alzheimer's disease, lupus erythematosus, or rheumatoid arthritis where overlapping clinical symptoms obscure molecular diversity integrative exosome-based omics can disentangle pathogenic pathways, enabling more precise diagnostics and targeted treatments.

6.2 AI/ML for Patient Stratification

Machine learning (ML) has emerged as a critical analytical tool in the exploration of proteomic datasets, particularly those derived from exosomes, due to its capacity to manage the complexity and high dimensionality of such data. Exosomes, classified as nanoscale extracellular vesicles, encapsulate a diverse range of proteins, nucleic acids, and lipids, rendering them rich molecular messengers that mirror cellular physiological states. Integrating ML into exosome proteomics facilitates the discovery of disease-specific biomarkers and enhances predictive modelling of disease trajectories, thereby propelling translational research and clinical implementation (Kumar, 2024).

In proteomic applications, ML addresses pivotal challenges across experimental design, data curation, and analytical pipelines by uncovering intricate relationships often overlooked by conventional statistical techniques (Kelchtermans *et al.*, 2014). The efficacy of ML in proteomic analyses is bolstered by access to expansive and high-fidelity repositories such as ProteomeTools and MassIVE-KB, which underpin the training of predictive models with improved generalisability (Dens *et al.*, 2024).

ML frameworks have been instrumental in accelerating high-throughput biomarker discovery, particularly in oncology, by refining the identification of tumour-associated proteins for early diagnosis, prognostic evaluation, and risk stratification (Fu *et al.*, 2024). Furthermore, deep learning advanced ML subclass has exhibited notable success in proteomics through applications such as chromatographic retention time forecasting, MS/MS spectral prediction, and protein structural inference, showcasing its adeptness at distilling abstract data representations from complex inputs (*Wen et al., 2020*).Despite these advances, considerable obstacles persist, including the standardisation of data formats and the development of transparent, interpretable models suitable for clinical validation (Adeyanju and Ogunjobi, 2024; Ahmad *et al.*, 2021). Nonetheless, the integration of ML into exosome proteomics holds substantial promise in refining patient stratification and driving molecularly tailored interventions central to the ethos of personalised medicine.

The utilisation of exosome-derived proteomic signatures, combined with unsupervised clustering, has shown efficacy in delineating patient subsets in autoimmune diseases. For instance, *Skogberg et al.* (2020) demonstrated that ML algorithms could stratify patients based on exosomal protein profiles, corresponding to variations in treatment response and disease progression. This aligns with findings in rheumatoid arthritis (RA), where *Ferreira et al.* (2023) applied unsupervised clustering to plasma proteomes, unveiling two clinically distinct RA subgroups with divergent TNF receptor superfamily expression. Likewise, *López-Pedrera et al.* (2022) used serum proteomics to differentiate systemic lupus erythematosus (SLE) phenotypes associated with nephropathy and inflammatory markers.

In multiple sclerosis (MS), *Gross et al.* (2023) identified immunological endophenotypes via blood-based proteomic profiling, which corresponded to disease progression rates and treatment responsiveness. Such studies underscore the capacity of proteomics-driven stratification to enhance disease classification and individualised therapeutic planning. Moreover, *O'Neil et al.* (2021) demonstrated that ML-enhanced proteomic models accurately forecasted RA flares, exemplifying the translational value of this approach. The recurrence of stratification patterns across autoimmune conditions implies the broader applicability of these techniques in precision immunology (Barturen *et al.*, 2020; Kruta *et al.*, 2024).

In oncology, the convergence of supervised ML techniques, including random forests, support vector machines (SVMs), and deep learning architectures, has advanced the development of robust predictive models for immunotherapy outcomes based on exosomal biomarkers such as PD-L1, CTLA-4, and tumour-associated antigens. These models enable dynamic refinement of predictions as additional exosomal data become available, supporting real-time clinical integration (Xie *et al.*, 2023; Sinha *et al.*, 2024).AI facilitates biomarker filtration, transforming extensive proteomic datasets into clinically actionable insights by isolating minimal yet highly informative biomarker panels. This streamlines assay development and facilitates regulatory approval (Arzumanyan, 2023; Olawade *et al.*, 2025). AI-driven models have demonstrated competency in predicting immunotherapy response, progression-free survival, and overall survival, particularly in malignancies such as non-small cell lung carcinoma (NSCLC), albeit with persisting challenges in data quality, interpretability, and reproducibility (Lu *et al.*, 2023; Erisa, 2024).

Additionally, AI contributes to the identification of novel therapeutic targets and optimises therapeutic regimens by triangulating proteomic data with genomic and transcriptomic inputs (Olawade *et al.*, 2025; Erisa, 2024). Ongoing efforts to develop interpretable AI tools aim to enhance model transparency and clinician trust, which are essential for regulatory and clinical adoption (Sinha *et al.*, 2024). Despite regulatory, ethical, and infrastructural barriers, the integration of AI/ML into exosome proteomics remains a transformative avenue for realising the goals of precision oncology (Li *et al.*, 2024).

6.3 Clinical Decision-Support Systems (CDSS)

The integration of exosomal proteomics into precision medicine reaches its critical operational threshold with the implementation of clinical decision-support systems (CDSSs). These digital platforms synthesise patient data, encompassing electronic health records, imaging, genomic information, and now proteomic signatures, to generate evidence-based clinical recommendations. By cross-referencing individual patient profiles with a validated medical knowledge base, CDSSs assist clinicians in making accurate diagnoses, selecting optimal treatments, and determining appropriate follow-up actions (Osheroff *et al.*, 2012).

The inclusion of exosome-derived proteomic data into CDSS algorithms offers a transformative pathway toward individualised therapeutic interventions. For instance, elevated levels of exosomal human epidermal growth factor receptor 2 (HER2) in a patient with breast cancer may prompt the system to recommend HER2-targeted therapy such as trastuzumab, aligning treatment with molecular pathology (Gámez-Valero *et al.*, 2019). Similarly, CDSSs may detect high expression of resistance-associated proteins such as ATP-binding cassette sub-family C member 1 (ABCC1) within exosomal profiles, thus informing clinicians of the need for intensified monitoring or alternative therapeutic strategies (Kalluri and LeBleu, 2020).

Contemporary CDSS architectures increasingly incorporate machine learning (ML) models capable of adapting recommendations dynamically based on longitudinal datasets. These systems automatically update patient stratification or adjust therapy suggestions upon the acquisition of new proteomic data, such as from sequential liquid biopsies (He *et al.*, 2022). This adaptability enhances the real-time clinical utility of exosome profiling, enabling precision medicine to evolve with the patient's disease trajectory.

Additionally, the use of cloud-based, interoperable CDSS platforms facilitates data integration across institutions, expanding the scope for collaborative proteomics research and the refinement of artificial intelligence (AI) training datasets. Such infrastructure supports the transition of exosomal biomarkers from research tools to clinically actionable datasets, enhancing diagnostic specificity, therapeutic efficacy, and health system efficiency (van der Veer *et al.*, 2021). The fusion of exosomal proteomics with CDSS not only operationalises multi-omic data but also embodies the practical implementation of personalised medicine. Through rigorous data integration and real-time analytics, exosome-informed CDSSs hold the potential to significantly improve clinical outcomes by delivering tailored treatment regimens based on molecular evidence.

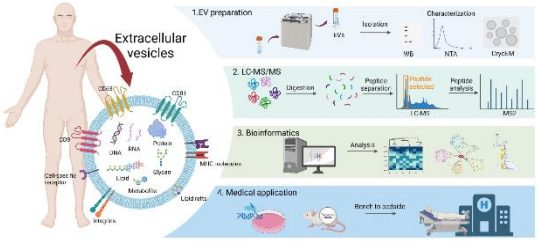

Figure 5: Exosomal Proteomic Integration in Clinical CDSS. (Source: Fan, S. and Poetsch, A., 2023. Proteomic research of extracellular vesicles in clinical biofluids. *Proteomes*, 11(2), p.18).

This figure presents a schematic overview of the clinical pipeline linking exosomal proteomic analysis to CDSS platforms. Beginning with patient biofluids (e.g., plasma, serum, urine), it shows exosome isolation followed by proteomic profiling via mass spectrometry. Detected biomarkers, such as HER2 or ABCC1, are then processed by a

CDSS engine, which integrates additional patient data (genomics, imaging, medical history). The system generates tailored recommendations, such as targeted therapy, surveillance protocols, or adjusted follow-up schedules. The illustration also emphasises ML-driven feedback loops: updated proteomic data from subsequent liquid biopsies refine patient risk stratification and therapeutic decisions in real time.

7. Challenges and Opportunities in Clinical Translation

As with other 'omics' technologies, the application of exosomal proteomics in personalised medicine presents substantial potential but faces considerable translational challenges. These include technical variability, regulatory uncertainty, infrastructural limitations, and the absence of scalable solutions. The clinical integration of these technologies requires a harmonised, interdisciplinary approach involving researchers, clinicians, regulators, and policy-makers to address the evolving landscape of diagnostic and therapeutic innovation.

7.1 Standardisation and Reproducibility

A significant bottleneck in translating exosomal proteomics into clinical practice lies in the lack of unified protocols that ensure analytical reproducibility. Although advances in mass spectrometry (MS) and isolation technologies have improved sensitivity and selectivity, disparities persist in the collection, purification, and analysis of exosomes across laboratories (Yanez-Mo *et al.*, 2015; Mateescu *et al.*, 2017). These methodological discrepancies impact not only intra-laboratory consistency but also the broader replicability of findings across institutions, impeding biomarker validation efforts. The MISEV2018 guidelines proposed by Théry *et al.* (2018) represent a cornerstone attempt at methodological harmonisation within the extracellular vesicle (EV) research community. These guidelines encourage the use of standardised terminology and advocate for orthogonal validation methods, such as nanoparticle tracking analysis, transmission electron microscopy, and immunoblotting for CD63, CD81, and TSG101.

However, widespread adoption remains incomplete, particularly in translational and clinical contexts, where rigorous implementation of quality assurance programmes (QAPs) is still lacking (Witwer *et al.*, 2021).The biological source of exosomes (e.g., plasma, cerebrospinal fluid, or urine) introduces additional variability in protein yield and purity, further complicated by inconsistencies in MS-based workflows such as enzymatic digestion, chromatography, and data analysis pipelines (Kalra *et al.*, 2012; Liu *et al.*, 2021). These limitations compromise the reproducibility of proteomic findings and hinder the development of universally accepted reference standards. Initiatives such as EV-TRACK (Van Deun *et al.*, 2017) have been instrumental in promoting transparency and encouraging standardised metadata reporting. Concurrently, commercial vendors have introduced validated exosome isolation kits and scalable analytical platforms to address reproducibility gaps. Efforts are also underway to establish centralised repositories of reference materials and exosomal protein markers, which are essential for inter-study comparability (Coumans *et al.*, 2017).

7.2 Regulatory Considerations for Exosome Diagnostics and Therapeutics

From a regulatory perspective, exosome-based diagnostics and therapeutics must navigate a complex approval landscape. For diagnostics, exosome-derived biomarkers must undergo rigorous analytical and clinical validation to meet the approval standards of regulatory agencies such as the FDA and EMA. These requirements include the demonstration of assay reproducibility across different sites, platforms, and cohorts - standards that many current studies fail to meet (Heath *et al.*, 2020). For therapeutic applications, engineered exosomes encapsulating siRNA, CRISPR-Cas9 elements, or pharmacological agents are regulated as biological products, necessitating Investigational New Drug (IND) and Biologics License Applications (BLA). These pathways demand extensive characterisation of batch consistency, immunogenicity, long-term safety,

and scalability. Furthermore, concerns persist regarding the bioengineering modifications applied to exosomes, which may affect their stability and biocompatibility (Antimisiaris *et al.*, 2021).

Despite these obstacles, recent developments signal growing institutional support. The FDA's Breakthrough Devices Program has expedited the review of liquid biopsy platforms that utilise exosomal content, fostering a more adaptive regulatory environment for novel diagnostic tools (Feng *et al.*, 2022). In parallel, industry-led initiatives are refining GMP-compliant exosome manufacturing and quality control systems, laying the groundwork for scalable clinical applications. In summary, while substantial hurdles remain, a confluence of standardisation initiatives, technological advancements, and evolving regulatory frameworks is gradually propelling exosomal proteomics from bench to bedside.

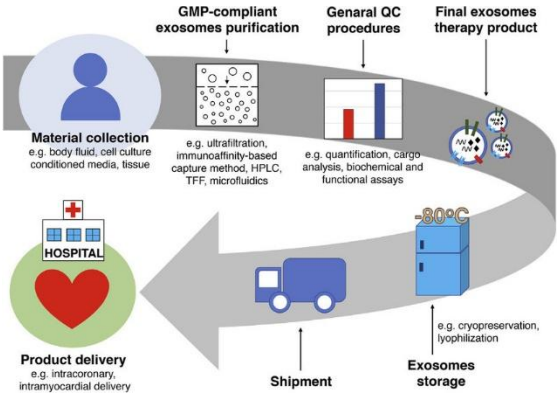

Figure 6: Translational Pathway of Exosomal Biomarkers from Discovery to Clinical Implementation. (Adapted from Adamiak, M. and Sahoo, S., 2018, "Exosomes in myocardial repair: Advances...")

This figure presents a comprehensive, circular flowchart detailing the stepwise translational pathway for exosome-based biomarkers. Starting at the discovery phase, candidate biomarkers are identified through proteomic and genomic analyses of exosomes isolated from relevant biological sources. Next, isolation and characterisation occur, using techniques such as ultracentrifugation, size-exclusion chromatography (SEC), nanoparticle tracking analysis (NTA), and Western blotting, to ensure high purity and vesicle integrity. In the analytical validation stage, methods like LC-MS/MS, quantitative PCR, or immunoassays are employed to confirm biomarker presence and function. The pathway progresses to clinical validation, involving large, multi-centre cohort studies to assess diagnostic and prognostic utility. Subsequently, regulatory approval is sought from bodies like the FDA and EMA, requiring rigorous data on assay reproducibility, multi-site consistency, and clinical effectiveness. Finally, successful biomarkers are implemented in diagnostics or therapeutics, enabling personalised medicine applications such as targeted drug delivery, disease monitoring, or stratified treatment planning. This visual highlights specific chokepoints, particularly in characterisation, validation, and regulatory alignment, where proactive intervention is essential to advance clinical translation.

7.3 Novel Approaches

Innovative platforms are now emerging to circumvent longstanding challenges in exosomal proteomics, including next-generation liquid biopsy technologies and microfluidic-based systems. These advances have significantly enhanced analytical sensitivity and enabled real-time, point-of-care biomarker detection, thereby improving clinical decision-making and patient outcomes. For instance, Chen *et al.* (2020) introduced a lab-on-a-chip device designed for the precise immunoaffinity capture and mass spectrometry-based analysis of exosomal proteins from peripheral blood. This integrated platform reduces sample processing variability and expedites throughput by eliminating the need for manual handling by multiple personnel. Its automation, scalability, and cost-effectiveness render it particularly attractive for both academic and clinical research environments. The integration of machine learning algorithms with exosome assays further amplifies diagnostic capability. These computational tools facilitate signal enhancement and biomarker identification by processing complex proteomic datasets to uncover subtle signatures predictive of disease onset, resistance to treatment, or recurrence. Such predictive modelling offers the potential for

highly individualised therapeutic interventions tailored to patient-specific molecular profiles.

Cross-disciplinary initiatives involving academic institutions, regulatory agencies, and private enterprises are increasingly forming collaborative frameworks to validate exosome-derived biomarkers. These public-private partnerships not only promote standardisation but also accelerate the development of clinical trials, regulatory approval processes, and long-term adoption. They serve as a crucial platform for harmonising best practices, establishing benchmarking metrics, and facilitating knowledge transfer across sectors. Although the implementation of exosomal proteomics in routine clinical settings is still hindered by regulatory complexities, reproducibility limitations, and methodological inconsistencies, recent progress provides grounds for cautious optimism. The adoption of consensus frameworks such as MISEV2018 (Théry *et al.*, 2018), advancements in microfluidics, and the evolution of regulatory guidelines tailored for biologics collectively signify a paradigm shift. These developments are driving the field towards clinically viable, scalable, and standardised protocols. As the molecular diagnostic landscape continues to evolve, exosome technologies are positioned to redefine precision medicine. Their capacity to provide deep, non-invasive molecular insights from treatment stratification to monitoring therapeutic response and disease progression, holds transformative potential. Ultimately, these emerging tools support a proactive model of care that is both patient-specific and dynamically responsive throughout the disease continuum.

8. Conclusion

The exploration of exosomal proteomics within the domain of personalised medicine continues to offer transformative prospects for disease diagnosis, prognostication, and therapeutic intervention. As highlighted throughout this review, the capacity of exosomes to encapsulate and transport proteins reflective of their cellular origin presents an unparalleled opportunity to decode complex pathophysiological processes in a minimally invasive manner. Their utility spans diverse clinical applications from early disease detection and therapeutic monitoring to real-time delivery of biomolecular interventions underscoring their potential as next-generation diagnostic and therapeutic vectors (Kalluri & LeBleu, 2020; Simons & Raposo, 2009).

Proteomic profiling of exosomes, enabled through advances in mass spectrometry and data analytics, has revealed nuanced insights into cell-cell communication, tumour microenvironment dynamics, and systemic pathological changes. Notably, the precision with which exosomes represent the proteomic landscape of parent cells makes them well-suited for stratifying patient responses, tracking therapeutic resistance, and enabling tailored treatment protocols (Yáñez-Mó *et al.*, 2015; Hoshino *et al.*, 2015). The integration of exosomal proteomics with multi-omics platforms, such as genomics, transcriptomics, and metabolomics, alongside machine learning and artificial intelligence, further amplifies their predictive and interpretive power (Cheng *et al.*, 2021).

Despite these advances, critical gaps remain. The field continues to grapple with reproducibility concerns due to heterogeneity in exosome isolation, inconsistencies in proteomic methodologies, and the absence of universally accepted reference standards (Théry *et al.*, 2018; Van Deun *et al.*, 2017). Moreover, regulatory frameworks for clinical-grade exosome deployment remain fragmented, with limited standardisation across jurisdictions and an urgent need for harmonised policy development. These limitations currently restrict the full clinical exploitation of exosome-derived protein biomarkers. However, ongoing efforts to address these limitations, including the establishment of global databases such as ExoCarta and EVpedia, and community led initiatives like EV-TRACK are accelerating the push toward methodological coherence and data transparency (Mathivanan & Simpson, 2009; Kim *et al.*, 2015). In parallel, innovations in exosome engineering, including surface protein modification and targeted loading strategies, are paving the way for personalised nanoscale therapeutics capable of delivering site-specific interventions with high precision and

reduced off-target effects (Luan *et al*., 2017; Vader *et al*., 2016).

Future advancements will hinge on the successful translation of these technologies into the clinical setting. This requires multi-centre validation studies, scalable and reproducible manufacturing pipelines, and investment in integrated diagnostics such as lab-on-a-chip platforms. Interdisciplinary collaboration among clinicians, biologists, data scientists, and regulatory stakeholders is essential to catalyse this translation. Finally, exosomal proteomics encapsulates a convergence of precision, adaptability, and innovation that aligns with the vision of personalised medicine. If methodological, regulatory, and translational challenges can be overcome, exosomes have the potential to transition from experimental entities into central pillars of modern medicine. As research matures, its integration into clinical workflows will not only revolutionise patient-specific healthcare but also contribute to a more predictive, preventative, and personalised therapeutic paradigm.

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