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Review Article

Exosomes Next-Generation Approaches in Breast Cancer: Nano Drug Delivery to AI-Based Prediction

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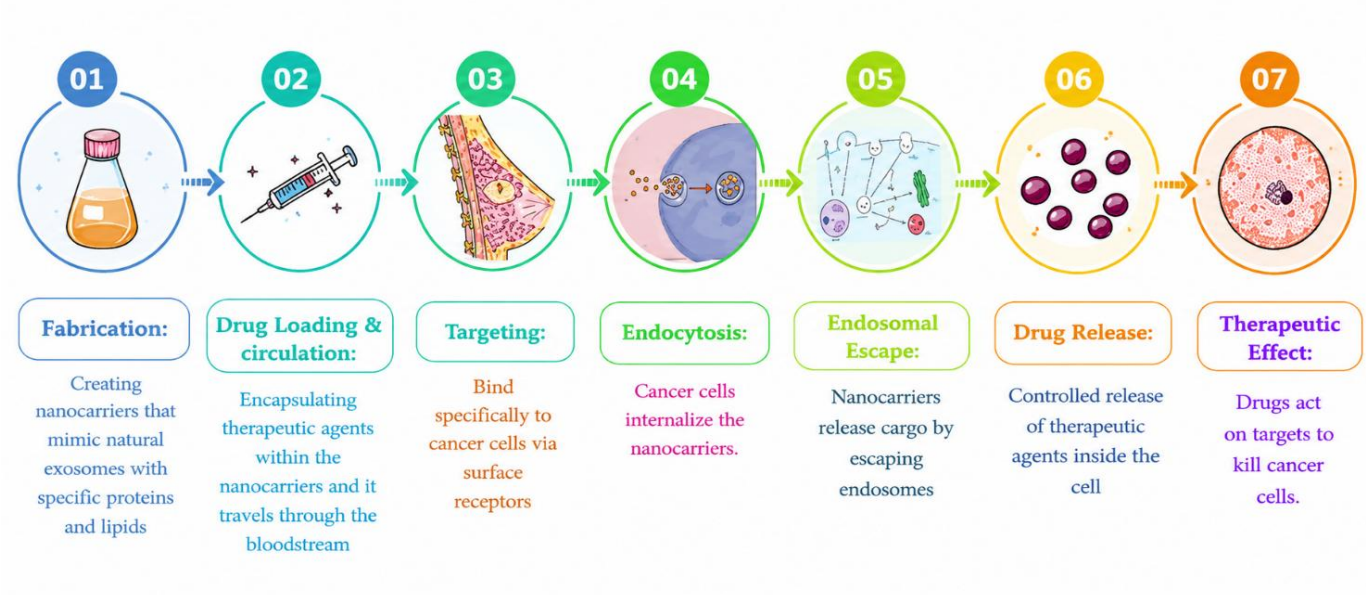
Abstract

Exosome mimetic nanocarriers have risen as a progressive biomimetic approach for intracellular drug delivery, exploiting the unique properties of natural exosomes to enhance therapeutic precision and efficacy. These synthetic vesicles imitate the structural, biochemical, and functional characteristics of natural exosomes, including lipid bilayer composition, surface proteins, and molecular cargo, offering superior biocompatibility, immune evasion, and targeted delivery capabilities. Unlike traditional nanocarriers, exosome mimetics exploit receptor-mediated endocytosis and natural cellular communication pathways to facilitate efficient intracellular transport and controlled release of therapeutic payloads such as chemotherapeutic agents, nucleic acids(siRNA, miRNA, mRNA) and proteins. Engineering strategies combine advanced liposome technologies with exosomal components to overcome challenges of yield, scalability, and immunogenicity, enabling customizable and reproducible drug carriers. This chapter comprehensively reviews the design principles, fabrication methods, and functionalization techniques of exosome-mimetic nanocarriers, emphasizing their advantages in precision oncology. Mechanistic insights into cellular uptake, endosomal escape, and tumor targeting are comprehensive alongside preclinical studies demonstrating enhanced antitumor efficacy and safety profiles. Furthermore, the chapter discusses translational hurdles, including standardization, large-scale production, and regulatory considerations. Integration with emerging artificial intelligence tools and multiomics theranostics presents future opportunities for optimizing nanocarrier design, patient stratification, and treatment monitoring. Overall, exosome-mimetic nanocarriers represent a transformative strategy in nanomedicine, poised to revolutionize intracellular drug delivery and enable precision personalized therapy in breast cancer and beyond.

Keywords: *Exosome, breast cancer, exosome-biomimetic nanocarriers, intracellular drug delivery, cargo loading, targeted therapy.*

Graphical Abstract



1. INTRODUCTION

Breast cancer (BC) is one of the most commonly diagnosed cancers in the world with 2.26 million new cases in 2020 [1]. its incidence and death rate have been steadily increasing over the last three decades, with breast, lung, and colorectal cancers collectively accounting for over half of all newly diagnosed cancers, with BC alone accounting for almost a third of cases [2]. About 25% of all female cancer diagnosis and nearly 25% of all cancer deaths worldwide are caused by BC, which continues to be the most common cancer among women and major cause of cancer-related mortality in terms of aggressiveness and clinical behaviour, BC exhibits significantly heterogeneity, which is primarily influenced by the origin site and molecular features of the together representing more than half of all newly diagnosed malignancies and BC alone accounting for nearly a third of cases [1]. Breast tumor is broadly divided into three major subtypes: Oestrogen Receptor-positive (ER+), Human Epidermal growth factor receptor 2-positive (HER2+), and triple-negative breast cancer (TNBC). ER+ tumors contain approximately 70% of all BC cases. The treatment of BC involves multimodal therapy, with surgery, radiotherapy, chemotherapy, and targeted approaches such as monoclonal antibodies, small-molecule inhibitors, antibody-drug conjugates, and immunotherapies [3]. Alongside, Metastasis is a critical problem, involving the spread of primary tumors to distant organs and contributing to treatment failure. Cancer stem cells are involved in both metastasis and resistance, owing to their self-renewal and differentiation capacity. Thus, innovative therapeutic platforms are under active investigation. Exosomes and biomimetic nanoarriers, owing to their biocompatibility and natural ability to cross biological barriers, have become a focal point in the search for next-generation treatments in BC [4].

The chapter offers information about natural exosomes, their biogenesis and structural components, along with isolation strategies, and it also explains exosome biomimetic nanocarrier, types, approaches, cargo loading, and their diagnostic and therapeutic applications.

2. EXOSOME BIOLOGY AND NATURAL ROLES

Exosomes are a specialised class of extracellular vesicles mainly released by eukaryotic cells, which play a central role in mediating intracellular communication. They are generally small in size (30-150nm diameter), characterized by a lipid bilayer, and originate from the endosomal pathway by the maturation of multivesicular bodies [5]. Exosome biogenesis is a process within cells that involves the inward budding of endosomal membranes and the selective sorting of cargo molecules. This results in the creation of intraluminal vesicles (ILs) inside early endosomes. Two major pathways regulate this process: ESCRT-dependent and ESCRT-independent mechanisms. In the ESCRT–dependent route, sorts and packages cargo through a stepwise assembly of ESCRT-0, -I, -II, and III complexes, with ESCRT-0 binding ubiquitylated proteins, and ESCRT-III, ultimately driving vesicle scission. Supporting proteins, such as Alix, assist in the sorting process [6]. Alternatively, the ESCRT-independent pathway relies on bioactive lipids, especially ceramides, to induce curvature and form ILs without ESCRT machinery. As endosomes mature into multivesicular bodies (MVBs), they either fuse with the plasma membrane to release ILs as exosomes or are directed to lysosomal degradation [7].

2.1. Exosome Structural Components

The structure of an exosome is simple at first glance, but each component plays a specialised role in determining how exosomes form, what they carry, and how they interact with other cells. At the core of every exosome is a lipid bilayer membrane, similar to the cell membrane but more tightly packed. This dense arrangement of lipids, proteins, and small RNAs, including miRNAs and non-coding RNAs, **Fig. 1** illustrates the major molecular components of exosomes and **Table 1** summarizes the core molecular components of exosomes and their roles.

Table 1. Major structural components of exosomes and their functional roles

Components	Examples/types	Roles and features	Ref.
Lipids	cholesterol, sphingomyelin, phosphatidylserine, ceramides, phosphatidylcholine, and phosphatidylethanolamine	Provides structural integrity, membrane curvature, cargo protection, and targeting capability	[5]
Proteins	Tetraspanins, heat shock protein integrins, annexins, ESCRT -accessory protein (clathrin, Alix, and TSG101), RAB family proteins, cytoskeletal proteins (actin, tubulin, myosin, radixin), histones, ubiquitin, MHC molecules	Biogenesis, cargo sorting, membrane fusion, cell adhesion, targeting, signaling, and immune modulation.	[5]
RNAs	mRNAs, microRNA, lncRNA, circular RNAs, and viral RNA	Post-transcriptional regulation in recipient cells, gene expression modulation, disease biomarker potential	[8]
DNA	dsDNA, ssDNA, mtDNA	Reflect, transmit, and influence the genetic and metabolic status of their environment	[8]

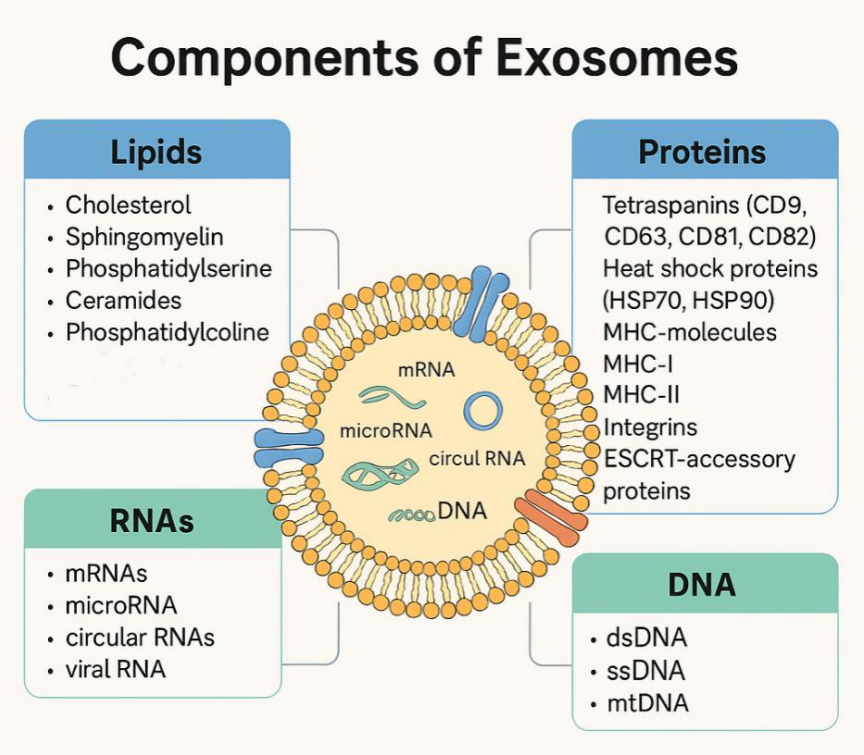


Figure 1. Structural components of exosomes

2.2. Origin-Based Types of Exosomes

Having outlined the key structural components of exosomes, it is equally important to understand that their functional identity is influenced by the cells they originate from. Classifying exosomes based on their origin offers deeper insight into their biological diversity and potential uses. They can be categorized into types such as dendritic cell-derived exosomes, tumour-derived exosomes, ascite-derived exosomes (Aexes), cytotoxic T lymphocyte (CTL)-derived exosomes, CAR (chimeric antigen receptor) T cell-derived exosomes, mesenchymal stem cell-derived exosomes (MSCs), and exosomes from natural sources. Each type has unique biological properties and functions, highlighting the diversity and therapeutic potential based on its source. **Table 2** outlines the major exosome types and their distinct immunological and clinical roles in cancer

Table 2. functional roles and clinical relevance of diverse exosome types in cancer immunology

Exosome type	Key functions	Clinical insights	Ref.
DC-derived exosomes	Activate tumor-specific cytotoxic lymphocytes, leading to cell death	Carry peptide/MHC complexes, CD80/83/86, induce T cell response and interferon secretion, promising for cancer immunotherapy	[9]
Tumor-derived exosomes	Carry tumor antigens, regulatory immunity	Contains MHC-I, HSP70, PD-L1, stimulates CTLs/NKs, but also inhibits immune cells and promotes Treg/MDSC expansion	[10]
Ascites-derived exosomes	Antigen presentation, immune modulation	Express MHC-I/II, CEA, ICAMs, can stimulate antitumor responses, and are used in initial trials with GN-CSF	[11]
CTL-derived exosomes	Mediate cytotoxicity against target cells via TCR-MHC interaction	Carry CD3, CD8, TCR, perforin granzymes, which can directly induce apoptosis in target cells	[10]
CAR-T cell-derived exosomes	Targeted antitumor cytotoxicity, safer alternative to CAR T cells	Release CAR- carrying exosomes for cytotoxic delivery, effective against TNBC models	[12]
MSC-derived exosomes	Apoptosis induction, immunomodulation,	Deliver galectin-1, immune cytokines, and miRNAs (miR-23B, miR-143) suppress BC migration, stimulates T/B/APC activation	[10]
Natural-derived exosomes	Communication, immune modulation, and biomolecule transport	Plant-derived edible nanoparticles are functionally similar but respond differently in the GIT	[13]

2.3. Natural Exosomes Isolation Techniques

Various isolation techniques are used to purify exosomes, such as ultracentrifugation, size-based filtration, size-exclusion chromatography, polymer precipitation, and ultrafiltration [14]. These are traditional methods suitable for pelleting lipoproteins, extravesicular protein, aggregates, and are not suitable for exosomal isolation from clinical samples due to their time-consuming, costly nature, and include many overnight centrifugation steps, mainly giving low yield and purity [15]. New techniques, like an immune-affinity purification and microfluidics-based innovations, meet the challenge of providing extremely pure exosomes for clinical settings. These new techniques utilize the usual separation determinants, like particle size, thickness, and immunoaffinity. Furthermore, these methods are quick and take fewer samples and reagents. The microfluidic devices trap exosomes with diameters between 40-100nm, separating protein, other EVs, and debris. These novel tools present fresh technical approaches and outlooks for improving the process of exosome isolation. Microfluidics works on the integration of microfluidic chips, acoustic/affinity separation, or inertial flow to isolate exosomes in miniature formats [12].

2.4. Exosome Functions in Cancer Progression and Therapeutic Signaling

Exosomes function as central players in breast carcinoma progression, effectively modulating key malignant features such as tumour growth, the invasive cell modification, the promotion of new blood vessel growth (angiogenesis), immune suppression, and therapeutic resistance. Angiogenesis is largely facilitated by intensive molecular communication, or crosstalk, that exosomes mediate between the BC cells and the surrounding endothelial cells. Tumour-derived exosomes further amplify this vascularization process by transporting pro-angiogenic molecules that specifically activate endothelial cells. Empirical evidence from both *in vitro* and *in vivo* models confirms that exosomal annexin II (A2), a calcium-dependent phospholipid binding protein, especially enhances angiogenesis in BC cells through a tissue plasminogen activator (tPA)-dependent mechanism [16]. Exosomal annexin A2 expression is markedly elevated in the serum of BC patients, especially African-American women with TNBC, and correlates with poorer clinicopathological features. *In vivo* Matrigel plug assays further demonstrate that TNBC-derived exosomes, Annexin A2 promote neovascularization [17]. Exosomes also contribute to immune evasion by transporting immunosuppressive molecules such as programmed death ligand 1(PD-L1) and OX40 ligand, which interact with T cells to suppress anti-tumor immune response and promote immune evasion [18].

Exosomal vesicles carry tumor-specific proteins, lipids, and nucleic acids (including miRNA such as miR-21 and miR-1246), and they serve as promising minimally invasive biomarkers. these vesicles can be isolated from patients' biofluids (blood and saliva), providing real-time insights into tumor subtype, stage, prognosis, and therapeutic response [19]. For example, elevated levels of exosomal miR-939 have been linked to basal-like TNBC and poor clinical outcomes. The emergence of exosome-based profiling offers strong potential for early BC detection, therapeutic monitoring, and individual therapeutic planning [19-20].

3. EXOSOME-MIMETIC NANOCARRIERS: CONCEPTS, TYPES, AND ENGINEERING STRATEGIES

Exosome mimetic nanocarriers (EMNs) are engineered nanoscale carriers designed to replicate the structural, biochemical, and functional characteristics of natural exosomes, and these are broadly classified into engineered exosomes (extracellular vesicles) and exosome mimetics [20].

3.1 Cargo Loading Strategies and Underlying Mechanisms

Exosomes have gained popularity recently due to their potential delivery system owing to their functional attributes. The cargo inside the exosome remains stable and does not undergo degradation, ideal for delivering tiny molecules. They can load natural cargos, such as miRNA, siRNA, DNA, and proteins, and release them to the targeted sites with accuracy. Strategies for drug loading contain incubation. A simple approach relies on the co-incubation of exosomes with tiny molecules for a long period and does not change the integrity of exosomes [24]. Sonication, where an ultrasound probe applies mechanical shear force to deform the exosome membrane and allows drugs to enter the exosome [25]. Electroporation involves the loading of small molecules through an external electric field, utilizing short high voltage pulses to remove the barrier of the membrane. Many other techniques are utilised, such as freeze-thaw cycle, transfection, extrusion, chimeric exosome method, and endogenous loading [23]. Extrusion, where exosomes and drugs are forced through nanoporous membranes, enhances drug integration. Freeze-thaw cycles promote drug incorporation by repeatedly disrupting and reconstituting membrane structure. Additionally, chemical conjugation, including hydrophobic interactions, covalent attachment, and click chemistry, enables surface display of therapeutic agents. Overall, the exogenous technique offers superior loading efficiency but may risk altering vesicle stability [26]. **Fig. 2** below illustrates the overall process of loading, isolation, and therapeutic application of EMNs

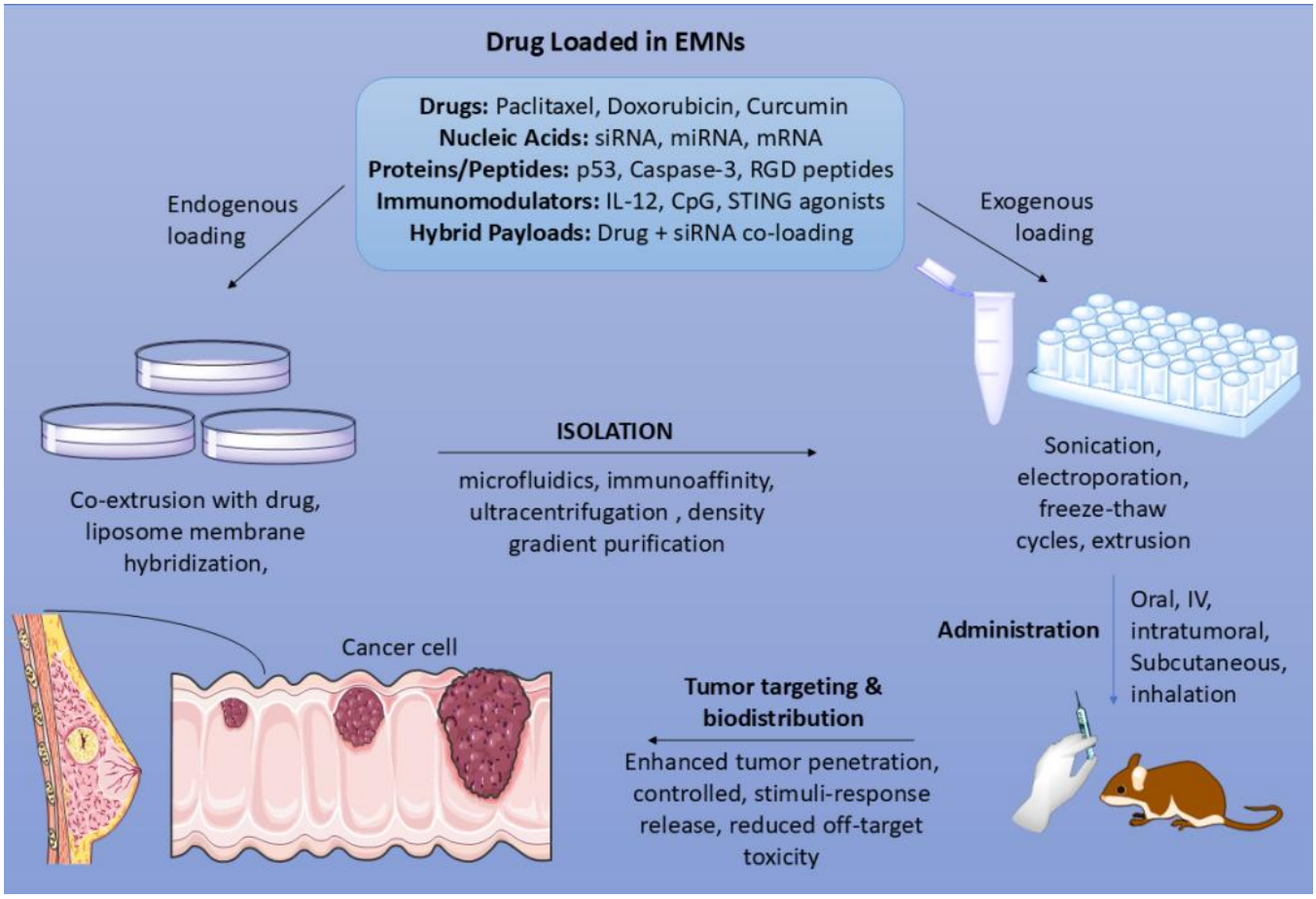


Figure 2. Overview of drug loading, isolation, and therapeutic application of Exosome-mimetic nanocarriers

The figure illustrates endogenous and exogenous strategies for loading diverse cargos into exosome mimetic nanocarriers, followed by key isolation methods and common administration routes used to achieve targeted tumor delivery and enhanced biodistribution.

3.2. Genetic and Surface Modification for Tumor Targeting

Genetic and surface modification of exosomes are advanced strategies to enhance their targeting ability and therapeutic efficacy against BC. Genetic modification is nothing but genetic engineering involves altering parental cells to express specific proteins or peptides on the exosome surface. Surface modification is surface chemical or biological modifications that enable attachment of targeting ligands, such as peptides, antibodies, directly onto isolated exosomes[27]. Genetically modified exosomes derived from mesenchymal stem cells(MSCs) have demonstrated effective targeting capabilities toward hormone receptor-negative or HER2-positive BC cell lines. Resulting in tumor death [28]. An exosome nanocarrier derived from miR-34a-overexpressing dental pulp mesenchymal stem cells (DPSCs) significantly reduced the migration and invasion abilities of MDA-MB-231 BC cells [29]. Additionally, exosomes from mesothelin-targeted chimeric antigen receptor (CAR) engineered with T cells offer a safer, effective BC immunotherapy by retaining parent cell features, such as CAR and CD3 expression, to target tumor cells specifically [30]. Adipose-derived stem cells (ADSCs) exosomes efficiently delivered miR-381 mimics to MDA-MB-231 BC cells, inhibiting their growth, migration, and metastasis while promoting apoptosis *in vitro* [31].

3.3. Comparison with Natural Exosomes and Traditional Nanocarriers

EMNs uniquely bridge the gap between natural exosomes and conventional synthetic carriers, combining the desirable biological properties of the former with the scalability of the latter. Clinical translation of natural exosomes is hindered by low isolation yield, batch-to-batch variability, and challenges in large-scale production. EMNs overcome these limitations by replicating the lipid composition, membrane topology, and functional surface proteins of exosomes using controllable engineering strategies [32].

Compared with traditional nanocarriers such as liposomes or polymeric nanoparticles, EMNs exhibit enhanced cellular uptake and reduced immune clearance due to biomimetic surfaces, improved membrane fusion efficiency. Their customizable architecture allows higher and more predictable drug loading, controlled release, and targeted ligand incorporation without compromising stability [33]. Thus, EMNs represent a next-generation drug delivery system that integrates the biological sophistication of natural exosomes with the engineering precision of synthetic nanocarriers. **Fig. 3** illustrates the major therapeutic advantages of EMNs in breast cancer

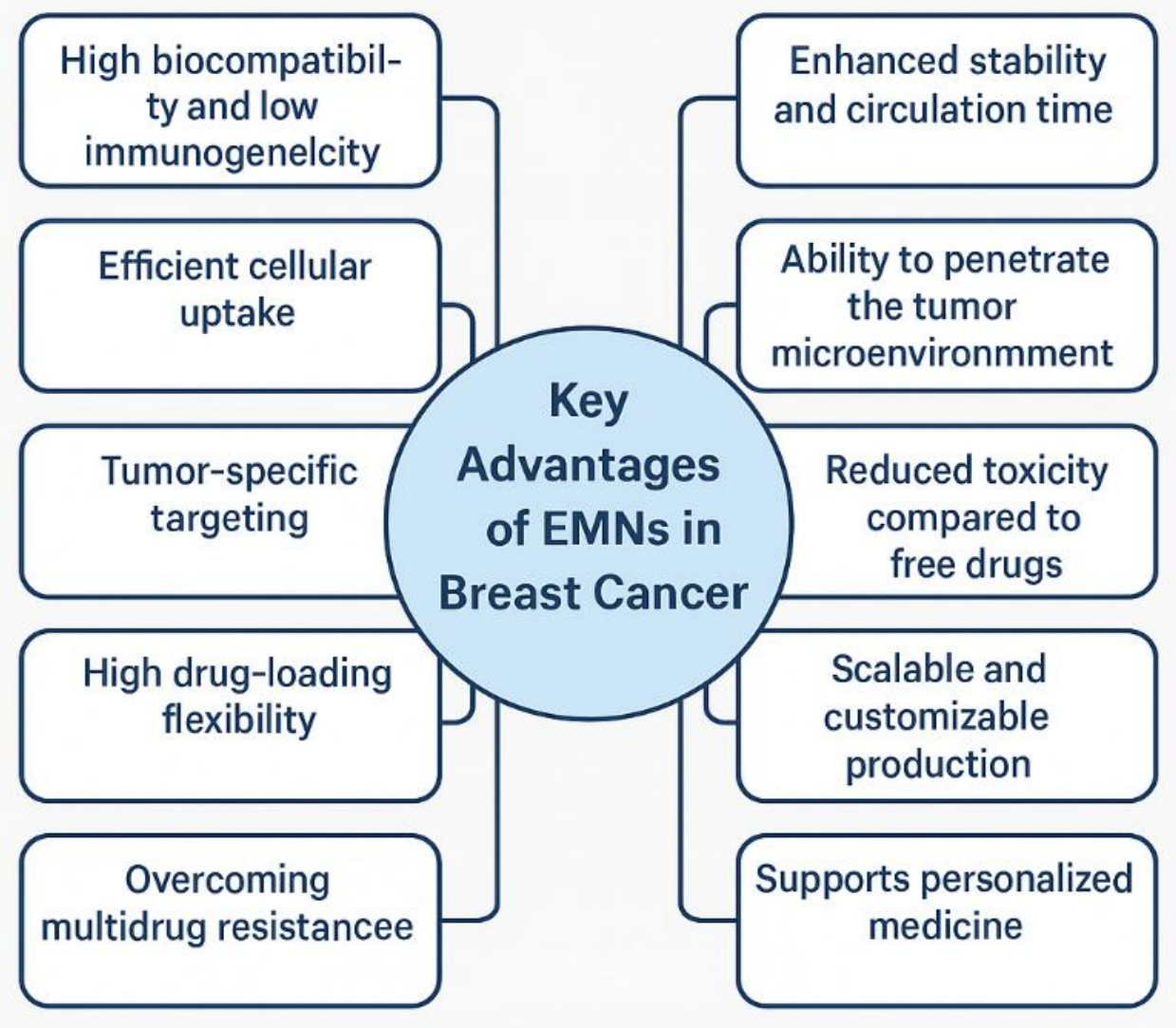


Figure 3. Key advantages of EMNs in breast cancer

4. FABRICATION AND CHARACTERIZATION OF EXOSOME MIMETIC NANOCARRIERS

4.1. Top-Down and Bottom-Up Approaches

EMNs are engineered vesicles designed to reproduce the biological behaviour of natural exosomes while offering greater flexibility in production and therapeutic loading. Their fabrication generally follows two major strategies: top down and bottom up, each providing distinct advantages for BC drug delivery.

Top-down approaches begin with whole cells, cell membranes, or large extracellular vesicles that are physically broken down into smaller, exosome-sized nanovesicles. Since natural exosomes originate from cells and share components, whole cells are used as a bulk starting material. Disrupting cells forms membrane sheets that self-assemble into vesicles with compositions highly similar to natural exosomes but with reduced heterogeneity. Common fabrication techniques such as serial extrusion through progressively smaller polycarbonate membranes, nitrogen cavitation, chemical-induced blebbing, and ultrasonication are commonly used [34].

Bottom-up approaches rely on assembling nanovesicles from basic building blocks such as lipids, polymers, and selectively incorporated proteins. Methods include thin-film hydration, microfluidic mixing, and solvent injection to create vesicles that structurally resemble exosomes. Targeting ligands, exosomal proteins, or membrane fragments may be added to enhance biological resemblance. Liposomes coupled with peptides, antibodies, membrane proteins, and coated polysaccharides can be beneficial in fabrication. For example, peptide-functionalised liposomes, where antigenic peptides are chemically attached to liposomal surfaces to mimic exosome-mediated activation of antigen-specific T cells, can be used. Hyaluronic Acid-coated liposomes were engineered to deliver paclitaxel via electrostatic interactions. CD44-rich cancer cells, leading to greater cytotoxic effect due to cellular uptake of biomimetic exosomes compared to both [35]. **Table 3** gives an overview of the methods used to fabricate EMNs, and highlights their relative efficiency, selectivity, and stability.

Table 3: fabrication approaches along with strengths and weaknesses

Techniques	Specific method	output	Cargo encapsulation	Vesicle stability	Ref.
Top-down strategies	Extrusion	High	Limited selectivity	Robust	[34]
	Sonication		Limited selectivity	Robust	
	Nitrogen cavitation		Limited selectivity	Robust	
	Membrane blebbing		Limited selectivity	Robust	
Bottom-up strategies	Liposome construction		High selectivity	limited	[36]
	Protein assembly		High selectivity	Robust	
	Synthetic vesicle design		High selectivity	Robust	
Biological methods	Virus-derived vesicles	Low	High selectivity	Robust	[37]

4.2. Key Physicochemical Characterization

During fabrication and characterization of EMNs, key physicochemical properties are systematically analysed to ensure optimal therapeutic performance and stability. Essential parameters include particle size and size distribution(by dynamic light scattering), surface area (zeta potential), morphology (using transmission electron microscopy or cryo-EM), and protein or lipid composition confirmed through techniques like western blotting or mass spectrometry. Further, drug-loading efficiency, encapsulation stability, and release kinetics are evaluated to confirm effective payload transport, while surface markers profiling helps verify biomimicry and targeting capability. Recent studies have demonstrated these analyses, such as dendritic cell-derived engineered exosomes for breast cancer[38] and hybrid exosome-based nanocarriers with enhanced characterization for immunotherapy [39].

4.3. Surface Ligand Engineering for Breast Cancer Targeting

Surface ligand engineering (SLE) focuses on adapting EMNs with carefully chosen ligands, such as targeting peptides, antibodies, or aptamers, to improve their ability to recognize and bind to BC cells. This surface tuning helps the nanocarriers home in on malignant tissue, reducing interaction with healthy cells. Chemically, biorthogonal click reactions like azide-alkyne cycloaddition are now widely used to snap ligands onto vesicle membranes under mild, aqueous conditions. For example, RGD peptides can be conjugated to exosome surfaces to recognize integrin receptors that are highly expressed on many BC cells, thereby improving targeting and uptake [40]. In parallel, genetic engineering of donor cells offers a more biologically integrated route to ligand display. Donor cells can be altered to express fusion proteins such as Lamp2b linked to HER2-binding peptides, which are then naturally incorporated into the exosomal membrane, providing selective affinity for HER2-positive BC. Similar strategies have been used to familiarize folate or other tumor-associated ligands, enhancing recognition by receptor-overexpressing cells.[41]. Together, these chemical and genetic approaches allow exosome-based nanocarriers to achieve more precise tumor targeting, higher rates of cellular internalisation, and better therapeutic performance compared with non-modified vesicles.

5. MECHANISM OF CELLULAR UPTAKE AND INTRACELLULAR DELIVERY

5.1. Endocytosis Pathways in Breast Cancer Cells

Endocytosis is the main route by which breast cancer cells take up EMNs, relying on several active internalisation mechanisms. These include clathrin-mediated and caveolin-mediated endocytosis, as well as micropinocytosis and, in some frameworks, phagocytic uptake [42]. The dominant pathway depends on how the EMN surface is engineered and on the receptor target cells. For example, EMNs modified with RGD peptides interact with integrins on BC cells and are proficiently internalised through clathrin-dependent, integrin-mediated endocytosis [40]. Caveolin-dependent uptake tends to occur rich in caveolae and can promote deeper trafficking of vesicles within the cytoplasm, whereas micropinocytosis permits bulk internalization of membrane and extracellular fluid, which is particularly useful for delivering deeply loaded vesicles [41-43].

5.2. Tumor Microenvironment Interactions (TME)

The tumor microenvironment interactions in BC are characterized by complex cell-cell interactions, the presence of extracellular matrix components, local factors, cancer cells, immune cells, and stromal cells of the local and distant tissues influence nanoparticle trafficking and efficacy. The interaction between cancer cells and their microenvironment plays a vital role in tumor proliferation, propagation, and response to therapies. EMNs have an inherent affinity for homing into tumor tissue via surface markers that mimic those of tumor-derived exosomes, facilitating cellular recognition within the TME. Studies have shown that engineered exosomes leverage cross-talk with stromal and immune cells to evade phagocytosis and promote localized delivery, while also responding to microenvironmental cues such as acidic pH and upregulated proteases, which activate drug release in situ [44]. TME interacts with traditional therapies like radiotherapy and chemotherapy, for example, HMGB1 can activate toll-like receptor 4 on dendritic cells to

cross-presentation of tumor antigen and activate subsequent cytotoxic T-cell response [45].

5.3. Overcoming Intracellular Barriers in Breast Tumor

Cellular entry of EMNs is done successfully but faces several intracellular obstacles, including endosomal sequestration, lysosomal degradation, and limited cytoplasmic escape. Advanced exosome engineering addresses these challenges by incorporating pH-responsive or membrane-disruptive elements, such as fusogenic peptides or proton sponge polymers, which facilitate endosomal escape and efficient intracellular delivery of payloads. Targeted ligand modification is used to enhance trafficking toward the cell nucleus or specific organelles, significantly improving therapeutic effect. The latest research highlights that such strategies enable robust gene silencing and cytotoxicity, even in drug-resistant BC models [46]. A notable study used exosome-sheathed mesoporous silica nanoparticles co-loaded with doxorubicin and 3,3'-diindolylmethane to treat TNBC. These hybrid EMNs demonstrated enhanced uptake and improved homing to cancer stem cells, resulting in reduced DOX-induced EMT compared to the free drug [47]. Thus, EMNs help overcome intracellular delivery blockages in breast tumors by combining biocompatibility, efficient uptake, and intelligent cargo release.

6. CLINICAL APPLICATIONS OF EXOSOMES IN BREAST CANCER

6.1. Exosomes as Diagnostic Biomarkers

Exosomes have gained significant popularity as diagnostic biomarkers in BC because they carry tumor-derived molecules that can be easily detected in blood, urine, and other body fluids. There are varieties of RNA and proteins that show diagnostic properties in recent studies, for example, surface proteins and a variety of enriched microRNAs reflect the molecular changes occurring in the tumour. Many of these markers, including glypican-1, surviving, miR-21,miR-1246, and miR-155, show consistent elevation in BC and help distinguish patients from healthy individuals. Some exosomal signatures are even associated with specific subtypes like TNBC or hormone-positive cancers. Owing to their stability and strong disease correlation, exosomes offer a promising, minimally invasive approach for early detection and monitoring of BC. **Table 4** summarizes key protein and miRNA biomarkers identified in BC and their diagnostic or prognostic significance.

Table 4: Exosomal biomarkers associated with breast cancer

Name of exosome marker (protein/miRNA)	Diagnostic relevance	Ref.
CD82	Increase in BC serum linked to disease progression	[48]
CD63	Combined with miR-21 in urine for BC detection	[49]
EpCAM, CD24	Ascites/effusion-specific for cancer exosomes	[50]
Del-1, fibronectin	Increased circulating exosomes in BC patients	[51]
Survivn	Prognostic/diagnostic marker in early BC	[52]
Glypican -1	Early exosome BC biomarker	[53]
Annexin	High BC serum linked to TNBC	[17]
miR-21, miR-1246	Significantly elevated in plasma /serum in BC	[54]
miR-145, miR-155, miR-382	Raised in BC vs healthy	[55]
miR-101, miR-373	Significantly high in TNBC	[56]
miR-223-3p	Elevated in BC linked to invasiveness	[57]
miR-16, miR-93	High in ER + BC	[57]

6.2. EMNs for Delivering Drugs, siRNA, miRNA, and Combination Cargos

EMNs facilitate precise delivery of chemotherapeutic agents, siRNA, and miRNA by mimicking natural exosomes while allowing engineered targeting and cargo loading. They shield sensitive nucleic acids from enzymatic degradation in the bloodstream and promote efficient cellular uptake via endocytosis [58]. Once delivered, siRNA or miRNA can regulate gene expression or silence oncogenesis, while chemotherapeutics act synergistically to kill cancer cells. Surface functionalisation with targeting ligands enhances selective tumor accumulation, minimizing off-target effects. Engineered exosomes have demonstrated outstanding results in delivering chemotherapy drugs, such as doxorubicin and 5-fluorouracil, as well as gene-silencing materials, including siRNA and microRNAs, either alone or in combination [59]. Several engineered exosomes and EMN-based formulations have been developed using drug cargos, targeting ligands, and fabrication strategies. **Table 5** summarizes key systems explored for targeted breast cancer therapy

Table 5: Engineered exosomes and EMNs used for targeted BC therapy

Encapsulated agent	Targeting domain	Preparation method	Recipient cell line	Function	Ref.
Dox(doxorubicin)	Platelet-derived markers(CD9/CD62)	Electroporation loading, ultracentrifugation isolation	MDA-MB-231 BC cells	Induce apoptosis (upregulation of Bax and annexin-V, and downregulation of Bcl-2) and reduce cell viability.	[60]
Dox	Dual peptides: iRGD+ tLyp1	Genetic engineering (HEK293F exosomes display), purification via tangential flow filtration and ultracentrifugation	MCF-7 and MDA-MB-231 BC cells	Significantly enhanced Dox uptake and cytotoxicity	[61]
Dox	iRGD peptide	Genetic (LAMP-2B)	Integrin-positive BC cells	Targeted chemotherapeutic delivery	[62]
Paclitaxel (PTX)	AS1411 aptamer	Chol -PEG2000	MDA-MB-231 BC glioma cells	Targeted anticancer therapy	[63]
Photothermal agents	RGD peptides	(DSPE-PRE-RGD)	Integrin-positive BC cells MCF-7	Photothermal therapy	[64]
miRNA-let7a	GE11 peptide	Genetic (LAMP-2B)	EGFR-expressing BC cells HCC70	Gene regulation and inhibiting tumor growth	[65]
MiRNA-9-5p	Tamoxifen-resistant exosome (from MCF-7/TAM)	Exosome-mediated transfer	MCF-7 BC cells	Increases resistance to tamoxifen, inhibits apoptosis, and downregulates ADIPOQ	[66]
SiRNA	DARP in G3(LAMP2b fusion, HER2-binding)	Engineered HEK293T exosomes (lentiviral transduction)	SKBR3 (HER2+BC cells)	Selective binding to HER2 ,delivery of siRNA, 70%TPD52 gene knockdown	[67]
HchrR6mRNA + prodrug CNOB	EVHB	Engineered extracellular vesicles EXO-DEPT	HER2-overexpressing BT474 cells,	mRNA delivery and prodrug activation, converting CNOB to cytotoxic MCHB in HER2 tumor	[68]
5-fluorouracil(5-FU)	Folic acid-chitosan(FA-CS)	HEK293 cell-derived exosomes (FA-CS-PEG-5FU)	MDA-MB-231 BC cells	Boosted anticancer effect, increased ROS, apoptosis/necrosis, minimal cytotoxicity to healthy cells	[59]
Verrucarin A (natural compound)	Anti-EGFR and anti-CD47 mAbs	HEK293F-derived exosomes	TNBC cell lines 4T1 mouse xenograft	Blocks tumor growth, high cytotoxicity	[69]
In situ DC vaccines(HELA-Exos)	Human neutrophil elastase (ELANE), Hiltonol(TLR3 agonist)	α-lactalbumin modified BC-derived exosomes	Mouse TNBC xenograft, patient organoids	Induced immunogenic cell death, strong tumor inhibition	[70]

6.3. Exosome-Based Nanoplatform Design for BC Therapy

Exosomes, when derived from functional or tumor cells, can serve as targeted coating substances or direct drug carriers. These cells have been utilized to construct smart nanoplatforms with enhanced tumor targeting capacity. For instance, EXO-GO-CO-γ-PGA-MIT, an exosome-coated bio-nanodrug that demonstrates slow drug release, tumor accumulation, and strong pro-apoptotic effects of mitoxantrone [71]. Radiolabelled exosomes tracers such as (11Iln) In-oxine-T-exosomes effectively visualised HER2-positive tumors[72]. Another system, EMPCs, integrated reactive oxygen species (ROS)-reactive paclitaxel conjugates and cucurbitacin B with exosome-decorated micelles to prolong circulation, enhance tumor penetration, suppress metastasis, and modulate FAK/MMP signaling [73-74]. Similarly, engineered macrophage exosomes modified with c-Met-targeting peptides (MEP-D) and siRNA-loaded exosome complexes (CBSA/siS100A4-exosome) displayed potent tumor-targeting and anti-metastatic properties [75]. Tumor cell-derived exosome mimetic porous silica nanoparticles (ID-E-MSNs) co-loaded with doxorubicin and indocyanine green enabled thermos-chemotherapy under near-infrared irradiation, achieving effective tumor ablation [76].

6.4. Recent Advances in Preclinical/Clinical Research

Badawy and coworkers demonstrated the therapeutic potential of milk and its exosomes against MCF-7 BC cells primarily by inducing apoptosis. The treatment increased pro-apoptotic markers and antioxidant enzyme activities, while decreasing inflammation, angiogenesis, and metastasis indicators. Camel milk exosomes had a stronger effect than camel milk alone [77]. Yang and coworkers developed doxorubicin-loaded biomimetic nanoparticles that showed enhanced targeting and controlled drug release in 4T1-luc BC cells, resulting in improved therapeutic efficacy and reduction of recurrence and metastasis [78]. Marshall and colleagues created red blood cell membrane-coated nanoparticles targeted to EpCAM-positive MCF-7 cells. These nanoparticles exhibited prolonged drug release and increased cytotoxicity, demonstrating potential as a theranostics platform for BC treatment [79]. Another study found that plasma exosomes augmented migration and invasion of MDA-MB-231 and MCF-7 BC cells by triggering FAK signaling, thus helping metastasis in these models [80]. Exosome-focused clinical trials in BC are listed in **Table 6,** outlining their objectives, design, and clinical relevance.

Table 6: Exosome-related clinical trials in breast cancer

Clinical trial title	NCT number	Study focus	application
Analyses of exosomes in CSF for BC patients with suspicion of leptomeningeal metastasis	NCT03974204	Evaluates CSF exosomes for diagnosing leptomeningeal metastasis in BC	Diagnostic
HER2-HER3 dimer expression in tumor and exosome samples of HER2+ BC patients	NCT04288141	Measures HER2-HER3 dimer in tissue and exosomes during HER2-targeted therapy	Predictive /monitoring biomarker
Exosomes as prognostic and predictive biomarker in early BC	NCT05955521	Studies exosomal cargo as biomarkers for therapy response	Prognostic/predictive biomarker
Feasibility of exosome analysis in CSF for suspected leptomeningeal metastasis in BC	NCT05286684	Feasibility of isolating and analyzing exosomes from CSF	Diagnostic feasibility study
Genetic characteristics of metastatic BC	NCT04258735	Includes exosome, ctDNA, RNA-seq analysis for genomic profiling	Molecular characterization
Clinical validation of plasma circRNAs hsa_circ_001785 and hsa_circ_100219 in BC	NCT05771337	Validating circRNAs for early detection	Diagnosis and disease monitoring
A pilot study of tumor-derived exosomes as diagnostic and prognostic markers in BC patients receiving neoadjuvant chemotherapy	NCT01344109	Assesses tumor-derived exosomes for diagnosis and prognosis during neoadjuvant therapy	Diagnostic/prognostic
Omic technologies to track resistance to palbociclib in metastatic BC	NCT04653740	Uses exosomes and multi-omics to study drug resistance mechanisms	Diagnostic
Impact of group psychological interventions on extracellular vesicles in people who had cancer	NCT04298398	Studies EV / exosome changes after psychological interventions	Biomarker modulation

7. AI-DRIVEN ENGINEERING OF EMNS IN BREAST CANCER THERAPY

Artificial intelligence is speedily becoming a driving force in refining the design and beneficial performance of EMNs for BC treatment by integrating multi-omics data, tumor microenvironment properties, and medical imaging features. AI allows the accurate and lucid engineering of EMNs with improved functionality. Machine learning (ML) models, such as support vector machines and random forests, can scrutinize patterns in drug response and exosomal biomarker countenance to recognize the most effective therapeutic cargos for encapsulation [81]. Deep Learning frameworks, including convolutional neural networks, simulate EMN behaviour under different biological conditions, for example, different pH, receptor properties, or vascularity, enabling scientists to forecast and fine-tune membrane composition and drug release rates. Likewise, transformer-based models proficient of handling enormous genomic and proteomic datasets simplify personalized EMN design by linking specific patient molecular signatures to customized Nanocarrier properties [82].

Beyond design, AI-driven optimization also boosts fabrication developments by refining limitations such as extrusion pressure, microfluidic shear, and membrane remodelling intensity. These data-guided alterations enhanced EMN size uniformity, structural steadiness, and duplicability across production batches [83-85]. Altogether, AI-enabled inventions are accelerating the transition toward an influential, scalable, and patient-tailored EMN system that holds substantial promise in progressing BC therapeutics. **Fig. 4** shows an AI-driven design of exosome-mimetic nanocarriers for precision breast cancer therapy.

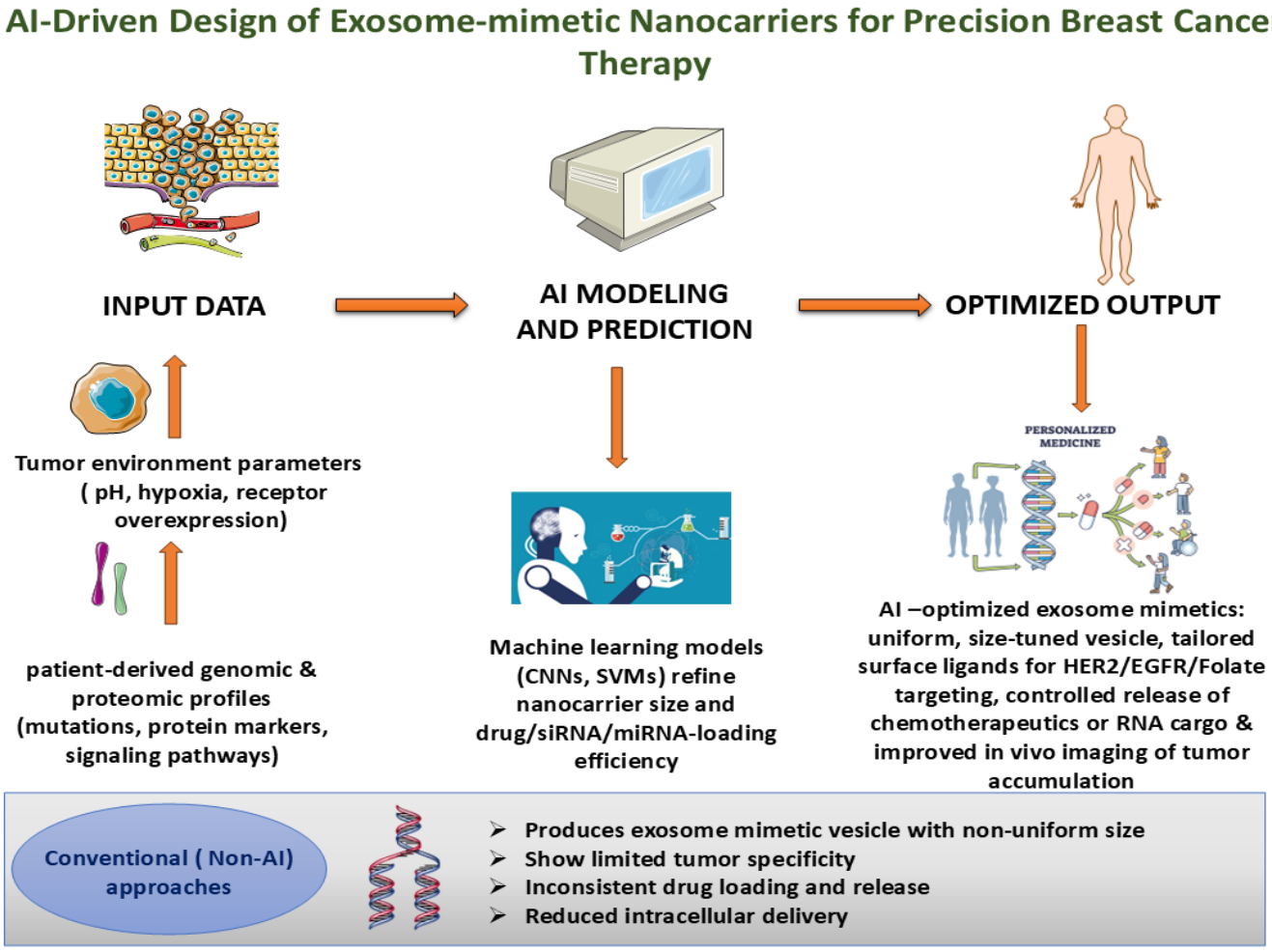


Figure 4: AI-driven design of exosome-mimetic nanocarriers for precision breast cancer therapy

FUTURE PROSPECTS AND CONCLUSION

EMNs are the latest and innovative platform in breast cancer (BC) therapy, merging the biological benefits of natural exosomes with the customizable nature of synthetic nanotechnology. As research progresses, new directions are emerging that could influence their clinical use. By using patient-derived exosomes or specially designed EMNs tailored to the molecular profile of individual tumors, and can create truly personalized nanocarriers for targeted delivery of drug-gene combinations. These personalized systems could address heterogeneity-driven therapeutic resistance, a key challenge in BC management. EMNs with tumor-

specific ligands, immune-modulating features, or gene-editing tools like CRISPR/Cas could selectively destroy resistant tumor clones while reducing systemic toxicity. Combining EMNs with real-time liquid biopsies might enable ongoing tumor monitoring and therapy adjustments. The EMN's future depends on the application of scalable manufacturing, ethical considerations, and strong clinical validation. Innovations in microfluidics, automated bioreactors, and membrane-like synthetic vesicles provide promising options for large-scale production. Additionally, combining strategies may produce synergistic effects beyond single drug therapy. Overall, EMNs show great potential as next-generation nano therapies for breast cancer, especially when integrated with AI-driven design and personalized medicine. Continued interdisciplinary efforts will be vital to bring these innovations into routine clinical practice, making treatments more effective and tailored to individual patients.

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