



# Precision approaches in breast cancer: Integrating molecular profiling with targeted nanocarrier-based therapeutics

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## ABSTRACT

Breast cancer (BC) remains one of the most complex and heterogeneous malignancies, driven by intricate interactions among genetic mutations, hormonal regulation, and environmental influences. The World Health Organization reported approximately 2.3 million BC diagnoses in 2022, accounting for nearly 11.6% of all newly reported cancer cases worldwide. This review highlights recent advances in BC research, emphasizing the integration of molecular profiling with nanomedicine to advance precision oncology. We examine key hereditary risk factors, including mutations in *BRCA1*, *BRCA2*, *TP53*, and *PALB2*, in the context of genetic predisposition, risk assessment, and preventive interventions. Emerging diagnostic approaches such as liquid biopsies, circulating tumor DNA analysis, and next-generation sequencing are compared with conventional biopsy techniques, emphasizing their potential for minimally invasive, real-time tumor monitoring. Particular attention is given to nano-enabled platforms for enhanced biomarker detection. On the therapeutic front, targeted nanocarrier systems (liposomes, dendrimers, polymeric micelles, exosomes, and antibody–drug conjugates) demonstrate promise in improving drug bioavailability, site-specific delivery, and mitigation of systemic toxicity and multidrug resistance. We outline major translational challenges like tumor heterogeneity, immune evasion, and the complex tumor microenvironment. Looking ahead, the convergence of stimuli-responsive nanoplatforms, RNA-based therapeutics, and biomarker-guided treatment is anticipated to redefine the therapeutic landscape. Overall, this review provides clinicians and researchers with an in-depth understanding of the evolving molecular and nanotechnological strategies driving precision medicine in BC management.

## 1. INTRODUCTION

Breast cancer (BC) is the second most common cause of cancer-related deaths and the most frequently diagnosed malignancy among women worldwide [1,2]. It represents a

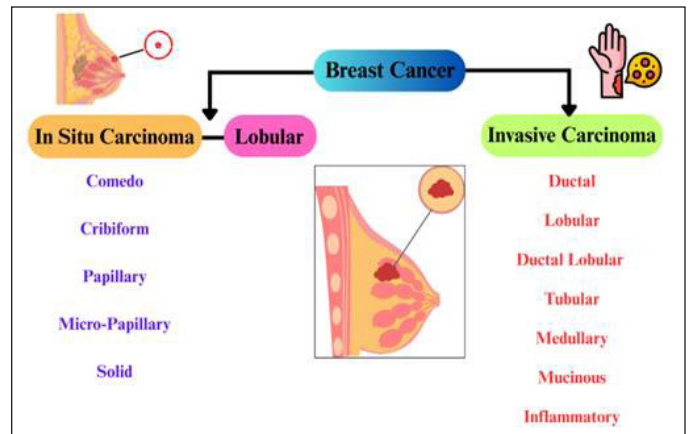
tumor arising from uncontrolled proliferation of abnormal breast cells that commonly originates in the milk ducts or lobules. Ductal carcinoma *in situ* is a noninvasive disease that may progress to invasive cancer, leading to metastasis by lymphatic or systemic dissemination [3]. Among the subtypes of BC, triple-negative breast cancer (TNBC) is the most aggressive type. It is characterized by the absence of all three receptors, namely, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), and accounts for about 10%–15% of all cases of BC [4,5]. It occurs predominantly in relatively younger, often premenopausal women, with higher prevalence in certain ethnic populations because of genetic and socioeconomic factors. In the absence of recognized molecular targets, limited therapeutic options result in early recurrence and poor outcomes. Recent molecular profiling has shown that

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TNBC is not a single entity but a heterogeneous group of diseases with distinct genomic and transcriptomic features. According to Lehmann's classification, the TNBC subtypes include Basal-Like, Mesenchymal (M/MSL), Immunomodulatory, and luminal androgen receptor, which are associated with targetable pathways such as DNA repair deficiency, androgen receptor signaling, and immune modulation. Key genomic alterations, such as BRCA1/2 mutations, Homologous Recombination Deficiency, activation of the PI3K/AKT pathway, and PD-L1 overexpression, underpin the need for precise molecular stratification. Despite promising treatments such as Poly (ADP-ribose) Polymerase inhibitors, immune checkpoint inhibitors, and antibody–drug conjugates (ADCs), clinical translation is still problematic due to tumor heterogeneity, resistance mechanisms, and the absence of reliable biomarkers. Integration of molecular characterization with nanocarrier-based precision medicine may help in the enhancement of subtype-specific therapy, minimization of systemic toxicity, and improvement of therapeutic efficacy [6]. Metastatic BC is the leading cause of cancer-related death among women. Approximately 99% of BC cases are seen in females, while males make up only 0.5%–1%, indicating female sex as a major risk factor [7,8]. In 2023, approximately 2.3 million new cases were diagnosed, which accounted for almost one-quarter of all malignancies in females [9]. In spite of advancement in screening and therapy, approximately 25% of the cases have still been found to behave aggressively and show unstable behavior that results in recurrence and metastasis. The other factors for disease susceptibility include age, history of reproductive events, radiation, and genetic predisposition [10]. Conventional treatments, like chemotherapy and radiotherapy, usually lack tumor specificity, leading to the destruction of healthy tissues and causing systemic toxicity. Although radioactive agents have long been part of cancer therapy, their application still remains limited due to adverse effects. Targeted therapies based on nanotechnology have increased precision and good biocompatibility. Organic nanocarriers include micelles, protein complexes, nanoemulsions, while inorganic ones include gold, magnetic, or iron oxide nanoparticles. In addition to conventional polymeric nanoparticles, advanced nanofibrous architectures have gained prominence for their high surface area, tunable porosity, and ability to integrate therapeutic agents [11,12]. Kumar *et al.* [13] developed a multifunctional polyvinyl alcohol nanofiber enriched with mulberry silkworm pupae oil and Prussian blue nanoparticles, demonstrating its strong biocompatibility and therapeutic potential in complex wound-healing environments. Recent studies have demonstrated that self-emulsifying nanoemulsion systems can significantly enhance the solubility and delivery potential of hydrophobic anticancer agents [14]. Developed and characterized a nonaqueous self-emulsifying nanoemulsion of curcumin, highlighting the efficiency of nanoemulsion platforms for biomedical applications. and quantum dots, all of which are capable of selectively delivering drugs to tumor tissues by attaching ligands on their surface [15]. However, the tumor microenvironment (TME)-which includes abnormal structure of vessels, dense extracellular matrix (ECM), and cellular diversity-delays nanoparticle penetration, hence reducing therapeutic efficiency. Recent developments in the field of engineered nanomaterials, especially bacteriophage-based



**Figure 1.** Histopathological overview of breast carcinoma progression. Illustration comparing *in situ* carcinoma with invasive carcinoma. Adapted from Hu *et al.* [16].

systems, have begun to demonstrate selectivity in eradicating cancer cells without affecting normal tissues, allowing targeted delivery and improving biomarker identification Figure 1. These intelligent nanotechnologies enhance therapeutic precision, reduce drug resistance, and decrease systemic toxicity, overcoming some critical deficiencies of traditional therapies. Finally, personalized nanotherapeutic approaches will go a long way toward optimizing patient outcomes and quality of life in the management of BC.

## 2. GLOBAL TRENDS IN BC INCIDENCE AND MORTALITY

World Health Organization's Global BC Initiative aims for a 2.5% annual reduction in BC mortality worldwide, a goal that requires vigorous data on interventions. In 2022, an estimated 2.3 million women were diagnosed with BC, and over 670,000 deaths occurred worldwide. Incidence rates are still on the rise worldwide, including in high-Human Development Index settings, although mortality has declined; few countries, however, are currently on track to achieve international goals for cancer control. Modeling predicts continued global disparities, including a 38% increase in incidence and 68% increase in mortality in low-HDI settings by 2025. These trends reinforce an imperative for strengthened surveillance, early detection, and access to care. Moreover, the age of diagnosis differs significantly around the world: while most cases are diagnosed after age 50 in high-income countries, diagnoses occur between ages 40 to 59 in many middle-income countries, including China, which suggests a need for region-specific strategies for screening [17].

## 3. GENETIC SUSCEPTIBILITY AND HEREDITARY BC SYNDROMES

Inherited mutations account for approximately 8%–10% of BC cases [18]. Roughly half of these involve *BRCA1* or *BRCA2*, while others are linked to less frequent mutations such as *PALB2*, *TP53*, and *CHEK2*. *BRCA1/2* Mutations occur in approximately 15%–20% of instances, predominantly in TNBC. In contrast, *BRCA2* and *PALB2* mutations are more common in hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-negative) subtypes [19].

Figure 2 depicts the key domains and pathogenic mutations of *BRCA1* and *BRCA2* associated with hereditary BC.

#### 4. ETIOLOGY AND RISK FACTORS OF BC: GENETIC AND ENVIRONMENTAL DETERMINANTS

It is a complex, ever-changing disease process driven by both genetic mutations and environmental influences. A graphical representation of these modifiable and nonmodifiable risk factors can be visualized in Figure 3. The path from the normal epithelium to invasive cancer involves several steps: hyperplasia, premalignant changes, and carcinoma *in situ*. This usually begins with genetic alterations, particularly in high-penetrance genes such as *BRCA1*, *BRCA2*, and *TP53*. Furthermore, according to the “two-hit” hypothesis, one inherited mutation is usually followed by another somatic mutation, and malignant transformation occurs. The risk of genomic instability or an additional “hit” is enhanced by exposure to estrogenic hormones or other carcinogenic substances, further driving the process of carcinogenesis. The earliest histological change is represented by ductal hyperplasia without atypia. The mutated cells, during the promotion phase, proliferate and interact with neighboring cells, promoting immune escape. Preinvasive lesions such as ductal carcinoma *in situ* are characteristic of this progressive process. The transition to invasive carcinoma occurs when additional genetic changes, along with interaction with the TME, allow cells to acquire aggressive behavior and a metastatic potential.

Visual overview of the genetic, hormonal, reproductive, and lifestyle factors that contribute to the risk of developing BC, following a design that points out modifiability versus nonmodifiability. Factors that elevate risk include early menarche, late menopause, nulliparity, low parity, delayed age at first childbirth, limited breastfeeding, and postmenopausal use of hormone replacement therapy. These reproductive and hormonal factors create a hormonal environment that is favorable to the development of cancer. Modifiable lifestyle habits that have strong links with an increased risk include obesity, physical inactivity, and excessive consumption of alcohol. Changing these practices can greatly reduce the chances of disease development. Genetic mutations in major genes such as *PALB2*, *TP53*, *BRCA1*, *BRCA2*, and *CHEK2* raise the hereditary risk of the disease. Precautions through personalized screening and prevention should thus be considered in cases of known genetic mutations or family history.

#### 5. MOLECULAR AND NANO-ENABLED DIAGNOSTIC INNOVATIONS IN BC

Conventional imaging modalities such as mammography, ultrasound, Magnetic Resonance Imaging, and histopathology remain the gold standards for BC detection and confirmation. However, these methods are often invasive, less sensitive in dense breast tissues, and prone to inter-observer variability. Molecular testing of *BRCA1*, *BRCA2*, *TP53*, and *PALB2* has improved hereditary risk detection, while liquid biopsies analyzing circulating tumor DNA and exosomes enable noninvasive disease monitoring. Recent nano-enabled diagnostic platforms have transformed the precision landscape. Gold-nanoparticle biosensors, quantum-dot

probes, and nanoparticle-based MRI contrast agents provide ultra-sensitive detection of tumor biomarkers such as HER2, ER, and Ki-67. Integration of nanodiagnostics with artificial intelligence (AI) analytics allows real-time, multiplexed tumor characterization with minimal invasiveness, bridging

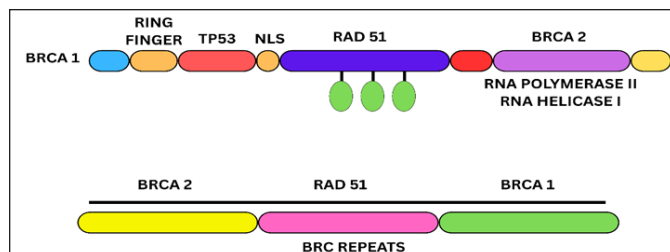


Figure 2. Functional architecture of *BRCA1* and *BRCA2* genes. An annotated schematic showing critical domains and mutation hotspots of *BRCA1* and *BRCA2* genes involved in hereditary BC predisposition. Adapted from Godet and Gilkes [20].



Figure 3. Comprehensive risk factors for BC development.

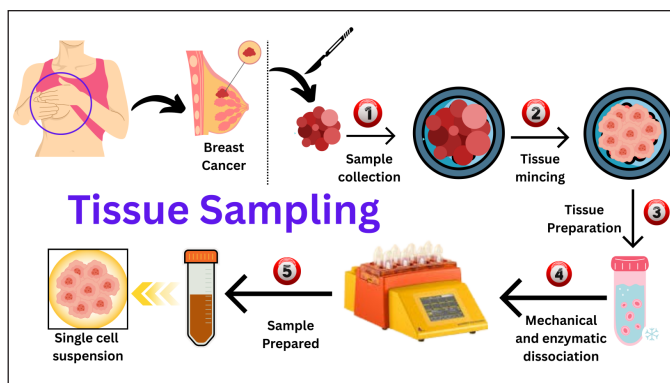
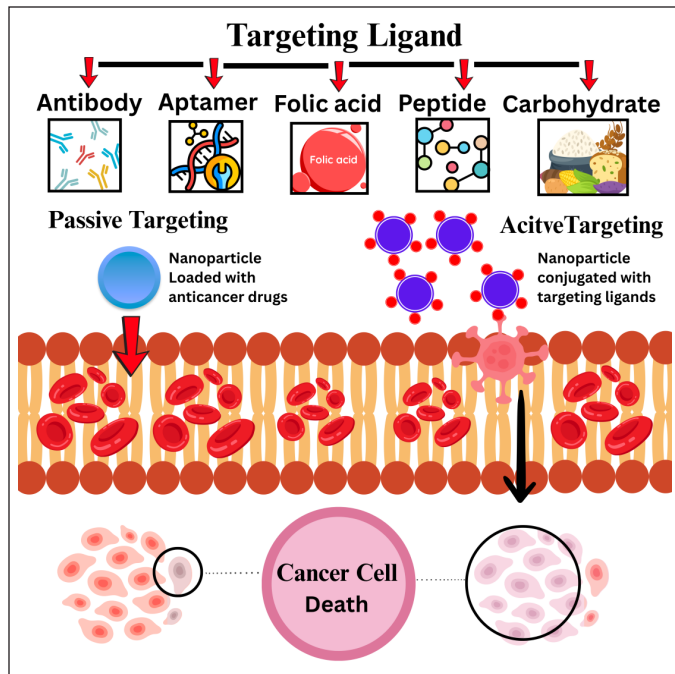
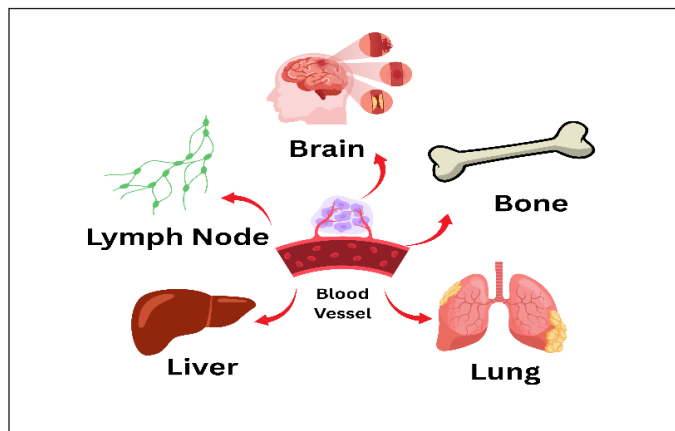


Figure 4. Techniques for breast tissue sampling in diagnosis.



**Figure 5.** Targeted nanocarriers in personalized therapy. Schematic depiction of nanoparticle conjugation with ligands (e.g., HER2 and folate) enabling active targeting in BC treatment.



**Figure 6.** Tumor cell plasticity and metastatic spread in BC. Depicts self-seeding and cross-seeding mechanisms of metastasis and how genetic instability leads to treatment resistance and inter-intra-patient variability in therapeutic response [67].

the gap between conventional imaging and personalized cancer diagnostics.

## 6. GENETIC TESTING AND RISK ASSESSMENT IN BC MANAGEMENT

Genetic testing has become a cornerstone of the evaluation of hereditary risk of developing BC, as it identifies familial variants that serve as strong indicators of an increased risk. These discoveries urge women to get tested for the purpose of early screening and diagnosis for themselves and their families. The most common variants with high

penetrance and risk include *BRCA1*, *BRCA2*, and *PALB2* [29, 30]. These patients are recommended to consider of risk-reducing surgical options and chemoprevention. Furthermore, options such as the Gail Model offer the stratification and estimation of risk based on family history. A substantially increased statistical risk is conferred upon the individual by inherited variants. Testing was previously reserved for those who had significant family histories of cancer and focused on a few known high-risk genes. In 2020, a comprehensive investigation covering 113,000 women discovered that BC was significantly associated with five protein-truncating variants-*ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*. Genetic discoveries such as these will provide a basis for finding appropriate screening and preventative measures, such as the use of risk-reducing surgery and pharmacotherapy, guided by national guidelines. Genetic testing, however, opens up ethical issues on distributive justice and equality of opportunity.

## 7. TARGETED NANOCARRIER SYSTEMS FOR PRECISION BC THERAPY

Over the past two decades, nanotechnology has become a crucial area of research in the development of advanced therapeutic strategies for BC. The use of nanomaterial-based pharmaceuticals offers notable advantages, particularly in minimising systemic toxicity and overcoming chemotherapy-induced drug resistance [29, 31, 32] Figures 4–8. Nanomedicines have shown promising therapeutic efficacy across various forms of BC. A wide range of nanoparticles, including liposomes, polymeric nanoparticles, micelles, dendrimers, and carbon nanotubes, have been explored for targeted drug delivery [31, 33, 34]. These nanoscale carriers enable both passive and active targeting mechanisms, allowing for more precise drug delivery to tumor sites while minimizing damage to healthy tissues. This targeted approach not only enhances therapeutic outcomes but also contributes to reduced adverse effects and improved patient tolerance. Among these nanocarriers, lipid-based systems, polymeric nanoparticles, and carbon-based nanostructures have shown particular promise despite ongoing concerns related to cost and long-term toxicity. Furthermore, the integration of nanomedicine with biomarker-based strategies opens new avenues for personalized treatment, potentially transforming the current landscape of BC therapy [34, 35].

## 8. ADVANCED STRATEGIES FOR TARGETED DRUG DELIVERY IN BC

Targeted therapeutic administration has emerged as a crucial component in the management of illnesses. The aim is to enhance the effectiveness of anticancer drugs while minimising their adverse effects on the entire organism. This strategy requires a comprehensive understanding of specific molecular targets and markers, particularly for BC, a complex disease characterized by diverse molecular profiles [48–50]. Identifying these critical disease-related attributes is essential for developing personalized therapy strategies and addressing the varied responses of individuals to this complex illness [51]. In addition, advancements in synthetic drug design and molecular modification continue

to play a central role in generating improved therapeutic candidates. Recent work by Haseen *et al.* [52] demonstrated the successful synthesis and structural characterization of novel sulfamethoxazole derivatives, highlighting the importance

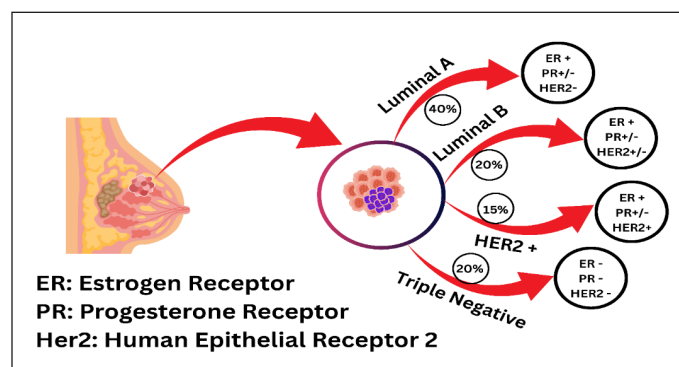


Figure 7. Schematic representation of TNBC in BC.

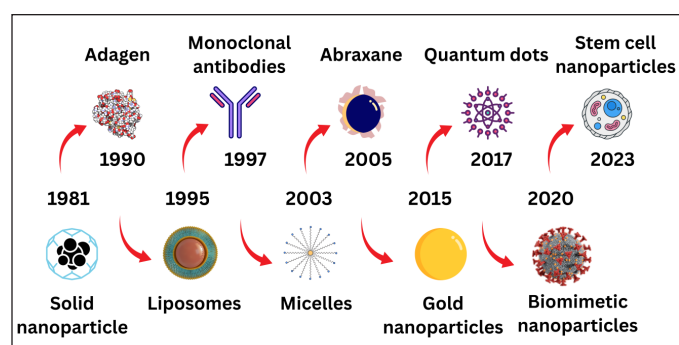


Figure 8. Overview of targeted drug delivery systems in BC. Visual pathway of drug delivery platforms (e.g., liposomes, ADCs, and exosomes) from administration to tumor targeting and release mechanisms [72].

of rational nanomolecular engineering in developing next-generation therapeutic scaffolds.

## 9. TARGETABLE MOLECULAR SIGNATURES IN BC

The introduction of molecular targets and biomarkers has entirely changed the way BC is treated. Hormone receptors, particularly ER and PR, are essential as their expression status aids physicians in selecting appropriate hormonal therapy [53]. Discovering HER2 as an important biomarker has also led to the development of effective HER2-targeted therapies, such as Herceptin, which have significantly improved the prognosis for individuals with HER2-positive BC [54]. Inhibitors of Cyclin-Dependent Kinase 4/6, palbociclib, ribociclib, and abemaciclib are CDK4/6 inhibitors that have become the standard therapy for advanced HR+/HER2+ BC. The PALOMA, MONALEESA, and MONARCH investigations demonstrated that these medications inhibit the progression of the cell cycle by obstructing cyclin-D–CDK4/6 activity. They significantly enhance survival. They effectively delay endocrine resistance and are frequently utilized in conjunction with selective estrogen receptor degraders (SERDs) and PI3K/AKT inhibitors. Researchers are investigating nanocarrier formulations of CDK inhibitors to mitigate blood toxicity and enhance tumor targeting. Recent advances in genomics have made it possible to see the many kinds of molecules that make up BC. These comprise luminal A, luminal B, HER2-enriched, and triple-negative subtypes. Each of these subtypes has its own genetic fingerprints, clinical paths, and drug sensitivities [55]. Identifying biomarkers associated with these subtypes is highly beneficial in developing personalised treatment plans that yield the best possible outcomes for patients [56, 57] Tables 1–4. Furthermore, understanding hereditary mutations like *BRCA1* and *BRCA2* not only helps to figure out who is at risk for BC, but it also helps to plan both preventative measures and tailored treatments. Ultimately, comprehensive molecular profiling holds significant promise in identifying novel targets for intervention

Table 1. Somatic and germline mutations in key tumor suppressor genes associated with BC.

Gene	Biological role	Representative mutations	Associated malignancies	References
<i>BRCA1</i>	Preserves genomic stability via homologous recombination, modulates cell cycle and tumor suppressor.	<i>185delAG, 5382insC</i>	Heredity of breast, prostate, ovarian cancer	[21]
<i>BRCA2</i>	Enhances DNA repair pathways via RAD51-mediated homologous recombination.	<i>5946delT, 771_775delTCAAA</i>	Breast, ovarian, prostate, pancreatic cancers; BC	[22]
<i>TP53</i>	Crucial regulator of DNA damage response and apoptosis; fundamental tumor suppressor.	Diverse somatic and germline mutations	Li-Fraumeni syndrome; breast, brain, adrenal, sarcomas, and various other solid neoplasms	[23]
<i>PTEN</i>	Inhibits PI3K/AKT signaling, enhancing viability and proliferation.	Multiple inactivating mutations	Cowden syndrome; malignancies of the breast, thyroid, endometrium, and kidneys	[24]
<i>CHEK2</i>	Promotes cell cycle cessation in reaction to DNA double-strand breaks.	<i>1100delC</i> (founder mutation)	Breast, colorectal, prostate, kidney, and other solid tumors	[25]
<i>PALB2</i>	Promotes cell cycle arrest in reaction to DNA double-strand breaks.	Truncating and missense mutations	BC and pancreatic cancer	[26]
<i>ATM</i>	Crucial for the repair of DNA, it plays a vital role in activating damage checkpoints.	Spectrum of pathogenic variants	Ataxia-telangiectasia (autosomal recessive); breast, ovarian, and other malignancies	[27]
<i>CDH1</i>	The preservation of architectural stability and epithelial integrity in tissues relies on E-cadherin.	Multiple germline mutations	Hereditary diffuse gastric carcinoma; lobular breast carcinoma	[28]

and enhancing patient classification. This will advance the field of personalised medicine in the management of BC [58]. Oral SERDs (Selective Estrogen Receptor Degraders) Novel oral SERDs have been developed to circumvent the issues associated with fulvestrant and the endocrine resistance induced by ESR1 mutations. Elacestrant, the inaugural FDA-approved oral SERD, as demonstrated in the EMERALD research, enhances progression-free survival in patients with ESR1-mutated HR+/HER2-malignancies. Other advanced medicines, including camizestrant, giredestrant, and imlunestrant, have robust ER degradation and favorable pharmacokinetics. These pharmaceuticals enhance the sensitivity of the endocrine system and exhibit efficacy in conjunction with CDK4/6, PI3K, and AKT inhibitors. This is a significant advancement in precision endocrine treatment. Inhibitors of the AKT and PI3K signaling pathways. Alterations in the PI3K/AKT/mTOR pathway enhance hormone resistance in HR+ BC. Alpelisib, a PI3K $\alpha$  inhibitor, and everolimus, an mTOR inhibitor, are two other pharmaceuticals that can selectively obstruct survival pathways. Nanocarrier-based delivery systems can enhance biomarker-guided therapies (PIK3CA, AKT1, and PTEN alterations) to reduce toxicity and increase specificity for malignancies.

### 9.1. Precision therapeutics in BC: ligand-directed and stimuli-responsive approaches

Advancements in specific drug delivery systems have significantly transformed the therapeutic landscape of BC. These targeted platforms enable the accumulation of therapeutic agents at the tumor site, thereby enhancing treatment efficacy while minimising systemic toxicity and side effects [59]. Modern drug delivery technologies not only help overcome multidrug resistance (MDR) mechanisms but also enable the precise modulation of the TME, thereby enhancing responsiveness to treatment. Among the most promising innovations are ligand-mediated nanoparticles, which enable receptor-specific targeting, and stimuli-responsive carriers, which release their payload in response to specific internal (e.g., pH and enzymes) or external (e.g., temperature and light) triggers [60]. This section explores recent progress in these advanced delivery systems, with a focus on their potential applications in clinical oncology. It also highlights emerging roles for these technologies in personalised medicine, where they can facilitate patient-specific treatment regimens and more effective tumor eradication [61].

### 9.2. Passive targeting via the enhanced permeability and retention (EPR) effect

Passive targeting strategies in BC therapy frequently exploit the EPR effect, a distinctive feature of the TME [62]. This phenomenon arises from abnormal angiogenesis commonly observed in solid tumors, including BC, where the neovasculature is structurally defective, characterized by disorganized, leaky, and highly permeable blood vessels. These pathological features facilitate the extravasation of nanoscale drug delivery systems into the tumor interstitium, where they tend to accumulate due to impaired lymphatic drainage [63]. The EPR effect thus enables the selective accumulation of nanocarriers in tumor

tissues, enhancing therapeutic concentrations at the target site while minimising systemic exposure. As a foundational principle in nanomedicine, the EPR effect underpins the design of numerous nanoparticle-based cancer treatments [64]. Leveraging this effect enables more efficient drug delivery, providing a passive yet effective approach to tumor targeting, particularly when combined with appropriate nanoparticle design and surface modifications to optimise circulation time and biodistribution.

### 9.3. Ligand and antibody-mediated active targeting systems

Active targeting represents a highly precise therapeutic strategy in BC treatment, employing molecular agents such as ligands, monoclonal antibodies, or peptides to guide drug carriers specifically to malignant cells [39]. These targeting moieties are selected for their strong binding affinity to receptors that are often overexpressed on the surface of cancer cells, including HER2, EGFR, and folate receptors [65]. By conjugating these ligands to nanocarriers such as nanoparticles, liposomes, or dendrimers, therapeutic agents can be directed to tumor tissues with increased specificity [66]. This receptor-mediated targeting facilitates enhanced cellular uptake through endocytosis, thereby improving drug accumulation within tumor cells while minimizing off-target effects. Active targeting significantly reduces systemic toxicity and protects healthy tissues from the harmful side effects commonly associated with chemotherapy and other cytotoxic treatments [15]. This approach forms a cornerstone of modern nanomedicine and personalized therapy, offering a promising avenue for more effective and safer BC treatments.

### 9.4. Site-specific metastasis: patterns and therapeutic challenges

Metastatic BC spreads in a predictable, organ-selective manner sculpted by the interplay between migrating tumor cells and the microenvironment of each organ. This compatibility is embodied by the classic “seed and soil” hypothesis, which explains why bone, lung, liver, and brain are the most common organs colonized by breast tumors. Chemokine signaling pathways, such as CXCL12/CXCR4, CCR7/CCL21, and CCR10/CCL27, provide a directional cue that steers tumor cells to supportive niches. For example, the high expression of CXCL12 in bone and brain promotes the adhesion and invasion of cancer cells by activating FAK, PI3K, and Rho-GTPase signaling. Brain metastasis represents an outstanding clinical challenge because the blood–brain barrier limits cellular access and prevents the majority of therapeutic agents from passing through. Tumor cells enhance BBB permeability through the release of factors such as MMP-2 and ANGPTL4 and engage in reciprocal interactions with astrocytes, microglia, and pericytes to establish a growth-promoting environment. The brain microenvironment further protects tumor cells through the induction of resistance to targeted and immune-based therapies. The elucidation of these organ-specific ecological relationships, therefore, requires precision treatment approaches. Improved nanocarriers capable of crossing the BBB include PEGylated liposomes, dendrimer-based small interfering RNA (siRNA) platforms, and exosome-like nanoparticles.

**Table 2.** Engineered nanocarriers with passive or active targeting strategies for BC.

Nanocarrier type	Surface ligand / coating	Targeting strategy	Payload	Application	Reference
Nanoemulsions	PEGylated hydrophilic surfactants (e.g., Kolliphore ELP)	Passive	Iodinated lipids	CT contrast agents for hepatic/splenic blood pool imaging	[36]
Dendrimers	PEG-conjugated RGD peptide	Active	AuNPs and Gd <sup>3+</sup> chelates	Dual-modality CT/MR imaging of malignancies that overexpress $\alpha\beta3$ integrins	[37]
Dendrimers	PEG-monomethyl ether and PEGylated folic acid	Active	AuNPs and Gd <sup>3+</sup> complexes	CT/MR imaging of folate receptor-expressing cancer cells	[37]
Polyethyleneimine (PEI)	PEG and siRNA (non-covalent complexes)	Active	Therapeutic siRNAs	Gene silencing in pulmonary tissues via RNAi delivery	[38]
Liposomes	Multifunctional peptide R8-RGD	Active	Paclitaxel	Brain-targeted drug delivery; preferential glioma accumulation	[39]
PEI-Gold NPs	PEI-PEG-monomethyl ether-folic acid	Active	AuNPs	Folic acid-mediated tumor targeting for CT imaging	[40]
Polymeric NPs (PLGA-PEG)	PEGylated cyclic peptide c(RGDfK)	Active	Cisplatin Pt(IV) prodrug	Targeted delivery to $\alpha\beta3$ integrin-positive prostate and BC cells	[41]
Polymeric micelles	Transferrin-modified PEG-phosphatidylethanolamine (Tf-mPEG-PE)	Active	R547 (CDK inhibitor)	Transferrin receptor-targeted therapy for ovarian carcinoma (A2780 cells)	[42]
Gold NPs	Anti-EGFR and anti-IgG functionalized PEG-AuNPs	Active	AuNPs	CT imaging of EGFR-expressing head and neck squamous cell carcinoma	[43]
Polymeric NPs	C18PMH-PEG	Passive	Fe <sub>3</sub> O <sub>4</sub> nanoparticles and doxorubicin	T2-weighted MR contrast and magnetically guided drug delivery (theranostic platform)	[44]
Gold NPs	Gum Arabic-folic acid conjugate	Active	Epirubicin and AuNPs	Targeted delivery of epirubicin to A549 lung cancer cells	[45]
Quantum dots	PEGylated nanoconjugates	Active	F3 peptide and siRNA	Fluorescent bioimaging and gene silencing (EGFP knockdown)	[46]
Lipid nanocapsules	Polysaccharide-based coatings (lipochitosan and lipodextran)	Passive	DiD fluorescent dye	Targeted fluorescence imaging in HEK293( $\beta3$ )-bearing murine models	[47]

**Table 3.** FDA/EMA-approved nanomedicine formulations for BC.

Nanomedicine (Trade name)	Drug agent	Nanocarrier type	Regulatory approval (Primary indication)	BC use	Key nanotechnology advantage
<b>Doxil® / Caelyx®</b>	Doxorubicin HCl	PEGylated liposome (~80–100 nm)	FDA (1995) – Ovarian cancer, Kaposi's sarcoma	Used in metastatic BC	Long circulation, passive targeting, reduced cardiotoxicity
<b>Abraxane®</b>	Paclitaxel	Albumin-bound nanoparticle (~130 nm)	FDA (2005) – Metastatic BC	First-line therapy for metastatic BC	Solvent-free delivery, higher dosing, albumin-mediated tumor uptake

### 9.5. TNBC: molecular profile and precision therapeutics

TNBC represents 15%–20% of all BCs and lacks ER, PR, and HER2 expression, resulting in limited targeted options and poor prognosis. It exhibits high molecular heterogeneity with frequent TP53 and BRCA1/2 mutations, conferring sensitivity to DNA-damaging agents such as platinum compounds and PARP inhibitors. A phase III trial demonstrated that carboplatin addition to taxane anthracycline neoadjuvant therapy improved survival (74.4% vs. 66.8% at 5 years) and pathologic complete response (54.5% vs. 40.3%). Immunotherapy combinations (pembrolizumab + paclitaxel–carboplatin, KEYNOTE-522) and nanocarrier-based systems liposomal doxorubicin, polymeric micelles, dendrimer conjugates, and exosomes, have shown superior selectivity

with reduced toxicity. Precision oncology in TNBC should integrate molecular diagnostics, immune modulation, and intelligent nanocarrier design to overcome inherent resistance and improve outcomes.

### 10. EMERGING TARGETED DELIVERY PLATFORMS FOR BC

Researchers are continually seeking more effective and accurate cancer treatments. This quest has led to the development of several new ligands targeted at drug delivery systems [59]. These high-tech platforms are designed to deliver therapeutic medicines directly to cancer cells, causing less damage to healthy tissues [68]. This segment offers an in-depth examination of the various types of targeted delivery

**Table 4.** Summary table approved & clinically evaluated nanomedicines.

Product (trade name)	Platform / composition	Active drug / MoA	Indication (approval / clinical status)	Notes / Clinical stage
Doxil / Caelyx	PEGylated (stealth) liposome	Doxorubicin	FDA (1995) / EMA (1996) used for BC, ovarian cancer, Kaposi's sarcoma.[83]	Classic example of EPR-based liposomal DOX.[84]
Myocet	Non-PEG liposome	Doxorubicin	EMA (2000) metastatic BC [83]	Non-PEG alternative for liposomal DOX.[84]
Abraxane	Albumin-bound nanoparticle (nab-paclitaxel)	Paclitaxel	FDA (2005) metastatic BC (also NSCLC, pancreatic).[83]	Widely used clinically; many ongoing/regional trials combining nab-paclitaxel.[84]
Genexol-PM	Polymeric micelle (mPEG-PDLLA)	Paclitaxel	South Korea (2007) approved for BC (regional).[83]	Example of micellar paclitaxel formulations.[84]
Lipusu	Liposome (lecithin/cholesterol)	Paclitaxel	China (2003) paclitaxel liposomal product (used for BC among others). [83]	Regional approval (China).[84]
Lipodox	PEGylated liposomal doxorubicin	Doxorubicin	FDA (2013) alternative liposomal DOX product.[83]	Often used as a generic/alternative to Doxil.[84]
Kadcyla (T-DM1)	ADCs (trastuzumab-emtansine)	Ado-trastuzumab emtansine (microtubule inhibitor payload)	FDA/EMA (2013) HER2+ BC (ADC).[83]	Protein-based nanocompound / ADC represents targeted bioconjugate class.[84]
Enhertu (trastuzumab deruxtecan)	ADC (trastuzumab linked to topoisomerase I inhibitor)	Deruxtecan (topo I inhibitor)	FDA/EMA/China (2019) HER2+ BC, expanded indications.[83]	Next-gen ADC with bystander effect.[84]
Trodelyv (sacituzumab govitecan)	ADC (antibody-SN-38 conjugate)	SN-38 (active metabolite of irinotecan)	FDA (2020) TNBC and other indications.[83]	ADC used in refractory TNBC. [84]
Pazenir (albumin-bound paclitaxel)	Albumin-bound nanoparticle (powder for dispersion)	Paclitaxel	EMA (2019) paclitaxel product (albumin-bound).[83]	Regional marketing authorization (EMA).[84]

technologies employed in oncology [69]. These include nanoparticle-based carriers, liposomal formulations, ADCs, and polymer-based systems [70]. Each of these advanced methods employs a distinct set of tools to enhance the effectiveness of cancer therapies. By looking into these new tactics, this conversation brings attention to the quickly changing world of targeted medicines that have a lot of potential to change how BC is treated [71].

### 10.1. Nanoparticle-based drug delivery systems

Nanoparticles are a powerful tool in targeted cancer therapy because of their ability to improve drug solubility, enable surface-based targeting, and provide controlled, stable drug release. In line with advancements in controlled-release technologies, polymer-based microsphere systems have demonstrated significant potential in improving drug retention and therapeutic efficacy. Developed gastroretentive floating microspheres of metaxalone, showcasing how polymeric micro-architectures can be engineered to achieve sustained release, high buoyancy, and enhanced bioavailability principles highly relevant to modern nanomedicine design [73, 74]. Their biocompatibility and ability to cross biological barriers make them suitable for precise and personalized treatment, including real-time monitoring and high cellular uptake. The Nanoparticles have revolutionized therapeutic strategies for BC. Albumin-bound paclitaxel, Abraxane®, represents a significant innovation in passive targeting and efficient delivery

of paclitaxel by reducing aggregation, enhancing its solubility, and decreasing systemic toxicity. Gold nanoparticles have shown strong tumor affinity and can be easily engineered for tailored *in vivo* behavior. Hybrid systems such as calcium phosphate-gold nanorod carriers enable controlled, pH-, and NIR-triggered release of doxorubicin. Magnetic nanoparticles allow for both imaging capabilities and magnetically guided drug delivery; chitosan-coated mesoporous MNPs loaded with doxorubicin have indeed demonstrated selective toxicity under alternating magnetic fields. Still, more emerging platforms like hollow copper sulfide nanoparticles are being refined to enhance photothermal therapy, intratumoral drug accumulation, and modify the TME to limit metastasis.

### 10.2. Liposomal formulations for site-specific delivery

Liposomes represent versatile, practical drug transport vehicles that confer a variety of benefits. They provide stability to drugs, prevent premature breakdown, and reduce toxicity at off-target sites by limiting exposure to normal tissues. Advanced engineering enables liposomes, biocompatible and biodegradable vesicles composed of lipid bilayers, to be prepared in various sizes to fit targeted and effective delivery. Their compartmentalized structure uniquely traps hydrophilic drugs within the aqueous core and protects hydrophobic drugs buried in the lipid membrane. Recent advances have enhanced liposomal formulations for accurate targeted distribution in BC treatment. Novel strategies involve complexing liposomes with

monoclonal antibodies that target overexpressed receptors. For example, liposomal doxorubicin conjugated with the anti-HER2 antibody trastuzumab increases drug delivery and therapeutic efficacy in HER2-positive BC.

### 10.3. ADCs: a novel targeted strategy

ADCs are a novel modality in cancer treatment because of their ability to target specific cells by directly delivering toxic drugs. As expected from this targeted delivery, systemic side effects, which are often associated with standard chemotherapies, are greatly minimized, thus increasing the possibility of treatment success. It was also envisioned that ADCs could overcome biological barriers and work with other treatments because an individualized cancer therapy is feasible. The ADCs are complex biopharmaceuticals that have a potent small-molecule medicine chemically linked to a monoclonal antibody through a specific linker. Success literally depends on the design of the linker and the choice of chemotherapy. Indeed, the first ever FDA-approved ADC, gemtuzumab ozogamicin (Mylotarg), was approved in 2000. Unfortunately, its hydrazone-containing linker was relatively labile in circulation, leading to premature drug release, systemic toxicity, and its subsequent withdrawal from the market in 2010. In contrast, sacituzumab govitecan-hziy (Trodelvy<sup>®</sup>) has achieved unprecedented clinical success targeting Trop-2-positive BC cells and has obtained regulatory approval. Clinical studies show it is effective in treating patients with resistant metastatic TNBC. HER2-Low Breast Carcinoma HER2-low disease (IHC 1+ or 2+/ISH-negative) has emerged as a distinct therapeutic category. The DESTINY-Breast04 trial demonstrated that trastuzumab deruxtecan (Enhertu) was superior in this cohort because of its elevated drug-to-antibody ratio, potent topoisomerase I payload, and bystander killing impact. Identifying HER2-low cancers expands the application of ADCs beyond only HER2-positive tumors, representing a significant advancement in precision-targeted therapy. This shift in perspective advocates for the development of next-generation ADCs optimized for tumors with moderate antigen expression levels.

### 10.4. Polymeric nanoparticles for enhanced therapeutic index

Several benefits make polymeric nanoparticles highly useful for targeted medication. They provide for regulated and steady drug release, which means that doses can be administered less frequently but still be equally effective. The modification of the surface enables targeting at distribution sites, hence minimal off-target effects and enhancement of overall therapeutic outcomes. They enhance the pharmacokinetic profile of drugs by their enhanced permeability at disease sites and/or reduction in systemic toxicity. Their versatility enables them to carry a wide range of therapeutic payloads, including proteins, genetic material, imaging chemicals, and hydrophobic medicines. Polymeric nanoparticles are suitable for clinical application in many medical fields due to their biocompatibility, ease of modification, scalability, and reproducibility.

### 10.5. Next-generation targeted delivery modalities

Alongside established platforms, several new targeted delivery methods are gaining rapid popularity in the treatment

of BC. These newer methods exploit the latest technology combined with a deep understanding of biology to render therapy far more precise and effective. Exosomes are small vesicles released by cells and are important in intercellular communication. They are generating considerable interest as natural vehicles of drug delivery in cancer therapy. Exosomes are ideal for targeted distribution because their surface proteins provide specific cell recognition and interaction, while the membrane lipid bilayer protects therapeutic cargo from degradation. Sustained circulation time further enhanced the efficacy of drugs. Exosomes are thus a promising approach to improving the efficacy and safety of cancer therapies. One such example is exosomes derived from M/MSL stem cells that have been prepared loaded with DOX. The addition of a targeting aptamer that specifically bound to cancer cells improved distribution precision and, as such, significantly reduced tumor size and increased survival rates in mouse models. New hybrid systems comprise inorganic nanoparticles with exosomes; in one example, cancer cells internalize mesoporous silica nanoparticles loaded with DOX and form core-shell complexes with exosomes, with considerable promise in animal models.

#### 10.5.1. Peptide-targeted therapies in BC

Peptides are short sequences of amino acids that specifically bind to receptors overexpressed on neoplastic cells and create tremendous interest for targeted treatment of BC. Scientists use such peptides as targeting ligands for drug-carrying nanoparticles or incorporate them into ADCs. This ability mediates the delivery of a drug straight to tumor cells while inflicting minimal damage on healthy organs and opens up great perspectives for personalized treatment according to the unique molecular profile of a certain tumor. Recently, several polyethylene glycol (PEG)-linked peptides were constructed that targeted specifically HER2-positive tumors and had enhanced metabolic stability. The research identified peptide sequences that targeted HER2 and more successfully penetrated and accumulated in the tumors.

#### 10.5.2. RNA-based therapeutics and delivery vehicles

RNA-based therapies, including siRNA and messenger RNA, are revolutionising BC treatment by enabling the precise targeting of genes and proteins crucial to tumor proliferation and metastasis [75]. Nanoparticle carriers can deliver these RNA molecules directly to BC cells, which is a potential method for silencing genes or altering protein production [76]. Several important research studies demonstrate the potential usefulness of this method. For example, tiny liposomes linked to specific proteins have been created to bind specifically to receptors that are present at elevated levels in BC cells [77]. This successfully delivers RNA mimics that block key signalling pathways that facilitate cancer spread. Other delivery techniques utilise polymer-based nanocarriers modified with aptamers to transport therapeutic RNA molecules and chemotherapeutic medications simultaneously [78]. This approach reduces the likelihood of tumor growth and makes treatments safer in preclinical animals. Furthermore, cationic liposomes designed to transport siRNA have demonstrated the ability to easily enter and remain in BC

cells, where they can silence specific genes with minimal harm to the cells [79].

### 10.5.3. Targeted immunotherapy: checkpoint inhibitors and delivery innovations

Immunotherapy is becoming an auspicious way to treat BC, especially aggressive types of the disease. Currently, researchers are attempting to deliver immune checkpoint drugs, including anti-PD-L1 antibodies, directly into the TME [80]. This targeted approach seeks to make immunotherapy more effective for BC by enhancing the immune response against tumors in the area and reducing side effects throughout the body [81]. The use of virus-like particles for the administration of the STING agonist 2'3'-cGAMP with outstanding accuracy is a significant step forward [82].

## 11. TRANSLATIONAL INSIGHTS: FROM BENCH TO BEDSIDE IN TARGETED BC THERAPY

It requires great effort and planning to turn ideas about targeted medicine delivery for BC into real therapies that doctors can use [83]. This approach starts with extensive preclinical investigations utilizing several lab models, followed by strict clinical trials with BC patients [84]. This section provides in-depth details on both the preclinical and clinical phases, highlighting critical developments, persistent problems, and significant achievements in targeted medication delivery for BC therapy [85]. The convergence of pathway-specific targeting and AI has transformed precision oncology. Therapeutics targeting the PI3K/AKT/mTOR, HER2/EGFR, RAS/MEK/ERK, and PARP pathways (e.g., alpelisib, trastuzumab, and olaparib) exemplify molecularly guided therapy. AI-driven omics integration supports early diagnosis, predictive modeling, and optimization of nanocarrier design. Despite its promise, implementation is limited by model bias, validation gaps, and infrastructural challenges in LMICs. Combining explainable AI with low-cost nanoplatfoms may address these translational barriers and enhance global precision medicine accessibility.

### 11.1. Preclinical advances in targeted drug delivery

Preclinical investigations are crucial in evaluating the safety and efficacy of novel targeted drug delivery systems [85]. Researchers frequently employ various laboratory models, such as *in vitro* cell cultures and *in vivo* models, to accurately replicate the TME and investigate the efficacy of therapeutic agents and their carriers within it. In this research, one of the primary objectives is to examine pharmacokinetics, biodistribution, and toxicity in detail [86]. Another goal is to see whether the delivery methods can target BC cells without harming healthy tissues [62]. Researchers also enhance carriers' features, such as particle size, surface modifications, drug release, and the addition of targeted ligands to maximise treatment efficacy [87]. Recent preclinical research continues to reveal that several sophisticated targeted delivery methods work well. They consistently demonstrate that drugs accumulate more effectively in tumor tissues, are more effective against tumors, and have fewer adverse effects on the body as a whole. These positive findings are the primary reason for advancing candidates into clinical development [69].

### 11.2. Clinical trials and therapeutic outcomes

Clinical studies are essential to establish the safety and efficacy of targeted drug delivery systems for BC treatment. These trials rigorously assess therapeutic effectiveness, patient tolerability, and applicability across various BC subtypes, including HER2-positive and TNBC [88]. Recent clinical advances have led to the approval of several targeted therapies. For example, the HER2CLIMB trial demonstrated the benefit of tucatinib in HER2-positive metastatic BC. In contrast, the ASCENT trial showed that sacituzumab govitecan significantly improved survival in patients with metastatic TNBC [89]. These breakthroughs have expanded treatment options and offered new hope to patients. Ongoing research focuses on refining patient selection, optimizing dosing regimens, managing adverse effects, and overcoming drug resistance. Future directions emphasize biomarker-driven personalization and combination therapies to further enhance the efficacy of targeted delivery systems in BC care [90].

## 12. CHALLENGES, BARRIERS, AND FUTURE DIRECTIONS IN TARGETED BC THERAPY

Significant barriers impede optimal targeted medicine delivery in BC, necessitating a coordinated effort to surmount them. This section examines these challenges from a scientific perspective and explores potential future directions based on empirical evidence and research findings [91]. Figure 9 illustrates a dual-targeted liposomal system capable of overcoming resistance and enhancing therapeutic efficacy in HER2-positive BC.

### 12.1. Overcoming biological barriers to enhance delivery efficiency

#### 12.1.1. Systemic barriers and nanocarrier clearance

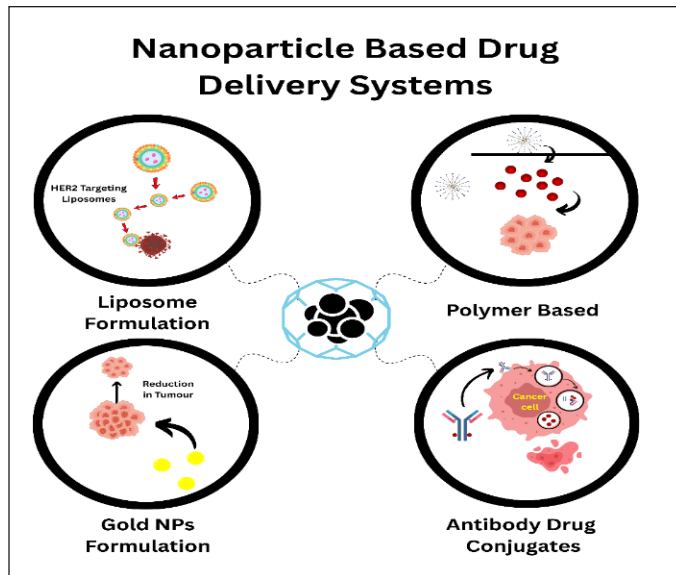
After being given via a systemic route, therapeutic drugs and their delivery vehicles have to go past the host's natural defensive mechanisms, which make it hard for them to clear [92]. The polymorphic phagocyte system (MPS) primarily functions in the liver and spleen. It quickly identifies and eliminates foreign nanoparticles through opsonization and phagocytosis. Surface engineering of nanocarriers with hydrophilic polymers, particularly PEG, has become a common approach to prevent rapid clearance from the bloodstream [93]. PEGylation shields particles from the immune system, allowing them to remain in the body longer by preventing protein corona formation and immune opsonization [94]. Another important constraint is that therapies do not always get where they are supposed to, which may lead to off-target accumulation and systemic toxicity. This demonstrates the importance of having highly selective targeting ligands that target tumors with greater specificity [95].

#### 12.1.2. TME: a therapeutic hurdle

Drugs must navigate a hostile TME that makes it hard to enter and spread. BCs have abnormal blood arteries that are irregular, leaky, and disordered, and their blood flow varies [96]. EPR effect makes passive accumulation easier.

Still, the different types of blood vessels often lead to unequal medication distribution and leave tumor areas that are low in oxygen and poorly perfused, untreated [97]. Leaky blood vessels and poor lymphatic drainage increase the pressure of interstitial fluid (IFP), creating an outer pressure gradient that

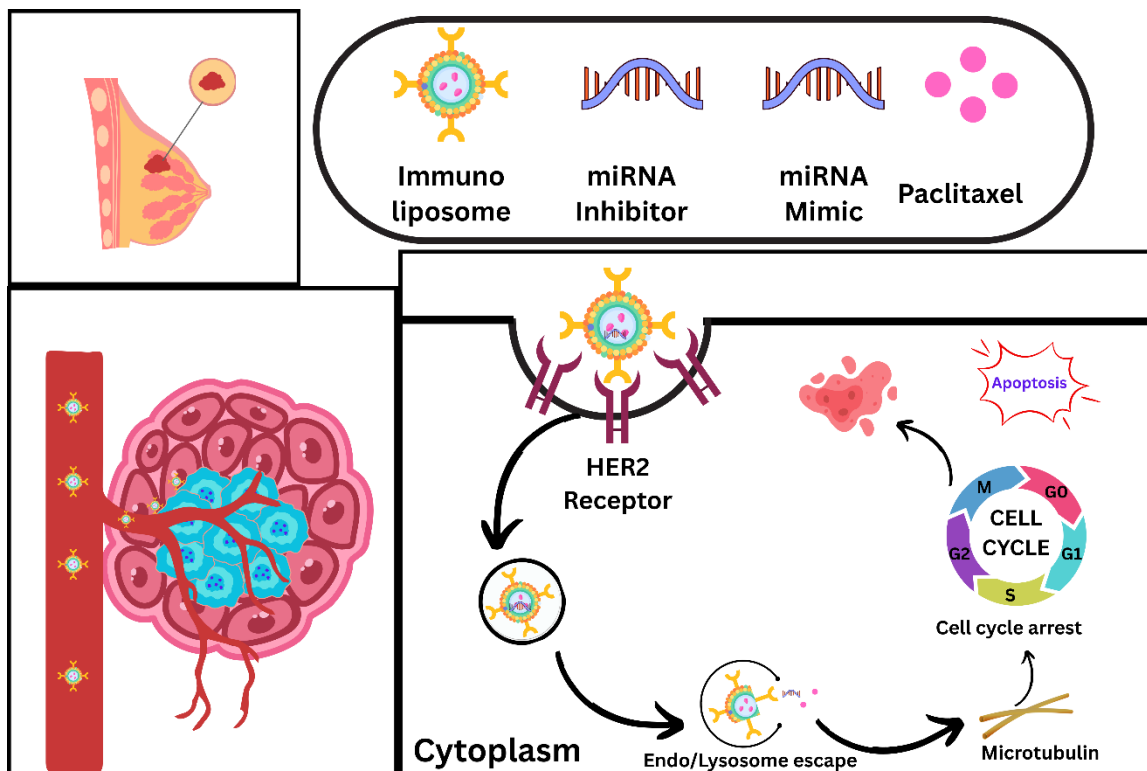
hinders the movement of drugs within the body [98]. Strategies to lower IFP, such as breaking down ECM components like hyaluronic acid using hyaluronidase or altering the permeability of blood vessels, have shown promise in improving medication delivery. The thick, fibrotic ECM, which is full of collagen, proteoglycans, and fibronectin, also functions as a strong physical barrier that keeps big nanocarriers from moving about by diffusion and convection [99].



**Figure 9.** Next-generation drug delivery strategies in BC. Emerging platforms, such as exosomes, stimuli-responsive systems, and multifunctional nanocarriers, offer enhanced selectivity and therapeutic efficacy.

12.1.3. Intracellular trafficking and endosomal escape

Even if a drug reaches a cancer cell’s surface, it may not be effective due to other obstacles within the cell. The cell membrane’s selective permeability makes it difficult for cells to take in large or charged molecules, such as proteins or nucleic acids [100]. Active targeting using ligands that bind to overexpressed receptors on neoplastic cells, such as HER2, EGFR, or folate receptors, enhances receptor-mediated endocytosis, allowing cells to absorb more of the drug [101] **Figure 10**. However, internalised agents often become trapped in endosomal and lysosomal compartments, where enzymes can break them down and render them useless. To release into the cytosol and maintain biological activity, it is important to have effective endosomal escape mechanisms [102]. These commonly include pH-responsive compounds or peptides that disrupt membrane integrity. ATP-binding cassette transporter proteins, such as P-glycoprotein, are another significant issue [103]. They aggressively push medications out of cancer cells, which makes them resistant to multiple treatments (MDR). Nanocarriers can bypass these efflux pumps by utilizing



**Figure 10.** Dual-targeted liposomes for co-delivery of miRNAs and chemotherapy. Demonstrates the strategy for overcoming HER2-positive BC drug resistance through co-encapsulation and targeted release.

alternative methods for cellular uptake or by simultaneously delivering efflux pump inhibitors, which prolong the retention of drugs within cells [104].

#### 12.1.4. Tumor heterogeneity and adaptive therapeutic strategies

BCs are quite distinct from one another, with differences at the genetic, cellular, and microenvironmental levels, both within individual tumors and across different patient groups. This variety makes it more challenging to develop targeted medicines that work for everyone. Instead, we need adaptive, individualised treatment plans or combinations of treatments that can work effectively on different types of tumors and in various environments. Overcoming this kind of diversity is crucial for achieving better treatment outcomes and reducing resistance [105, 106].

### 13. LIMITATIONS AND FUTURE PERSPECTIVE

Despite progress, biologic, translational, and regulatory hurdles continue to impede the clinical translation of targeted treatments for BC. Tumor heterogeneity, especially in TNBC, induces variable responses/resistance, thus requiring multitargeted nanocarriers to be engaged in combination therapies. The TME, characterized by a collagenous ECM and increased interstitial pressure, hinders homogenous drug distribution and thus requires the use of TME-modulating agents. Circulation time is reduced due to the rapid clearance by the mononuclear phagocyte system, which can be altered by biomimetic coverings such as cell membrane cloaking. Utilization of pH-sensitive polymers, with the co-delivery of efflux pump inhibitors, will help in overcoming endosomal entrapment and the resultant MDR. Stimuli-responsive and theranostic nanoplatfoms will be designed in the near future, which will integrate imaging and therapeutic functions for real-time drug release. Engineered exosomes, RNA therapeutics, and immunonanomedicine are new avenues that have shown outstanding selectivity, coupled with reduced systemic toxicity. However, scalability, chronic toxicity, and regulatory harmonization remain perennial challenges. Very recent systemic therapies, including ADCs (sacituzumab govitecan) and immunotherapy (PD-1/PD-L1 inhibitors), have revolutionized disease management in metastatic and TNBC. However, adaptive resistance, limited biomarker validation, and high costs limit universal access, particularly in LMICs. Integration of AI-driven therapy selection, nanocarrier-mediated delivery, and patient-centric care will be required to surmount these gaps. Future trials should be designed using adaptive, pharmaco-economically viable models to ensure equitable translation of novel therapeutics.

### 14. CONCLUSION

BC is one of the most heterogeneous malignancies, influenced by environmental, hormonal, and genetic factors. Due to improved diagnostics, such as core needle biopsies and germline testing, treating metastatic disease remains a challenge because of toxic side effects and lack of specificity. BC treatment has gotten a facelift from smart nanocarriers utilizing passive (EPR effect) and active (ligand/antibody-mediated) targeting mechanisms. Clinically approved

examples are represented by Doxil® and Abraxane®. However, translational restrictions remain significant, due mainly to tumor heterogeneity, nanocarrier optimization, and regulatory intricacies. Future prospects include the development of nanotechnology combined with molecular profiling to enable precision oncology. Multifunctional, stimuli-responsive systems, including exosome-based ones, are foreseen to power a new generation of treatments tailored for personalized, low-toxicity treatments. Translation of nano-enabled precision therapeutics needs multitiered collaboration between academic, clinical, and regulatory stakeholders. Key clinical trials such as HER2CLIMB (tucatinib), ASCENT (sacituzumab govitecan), and NAB-PAC (Abraxane®) represent successful clinical transitions. Future pathways need to be aligned with multiomics-driven patient stratification, AI-assisted formulation optimization, and adaptive clinical trial designs. Long-standing challenges include large-scale reproducibility, assessment of long-term nanotoxicity, and harmonization of international regulatory frameworks such as the FDA, EMA, and CDSCO. Furthermore, the establishment of globally accepted standards regarding the characterization and evaluation of nanomaterials would be essential to ensure the safety and accessibility of next-generation nanomedicine.

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All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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This study does not involve experiments on animals or human subjects.

### 19. DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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The authors declare that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI..

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