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Review Article

Developments in Small Molecule Therapeutics Targeted Drug Delivery Systems for the Treatment of Breast Cancer: Present Approaches

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ABSTRACT

This review aims to discuss the progress made in targeted drug delivery of small molecules in breast cancer, as well as the methods that can be used to increase the accuracy of the treatment and reduce the overall toxicity and resistance. In this work, we described nanoparticle-based drug carriers, antibody-drug conjugates, peptide-drug conjugates, exosome-based delivery and the current role of these systems in increasing the selectivity of the drug delivery to the tumor and drug bioavailability. Furthermore, we reviewed stimulus-controlled drug release systems, RNA-based co-therapies and AI-assisted drug design as the new strategies to enhance the effectiveness of treatment. Finally, we discussed the existing research needs and future trends in hybrid systems, personalized nanomedicine and large-scale production, which can help to understand the prospects of the next generation breast cancer therapies.

Keywords: WHO, TNBC, Chemotherapy, Research gap, MDR, Co-therapy.

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INTRODUCTION

Breast cancer is one of the most common cancers overall and the most frequent cancer among women and remains one of the most common causes of cancer related death among women. As reported by World Health Organization (WHO) and GLOBOCAN 2020, breast cancer was diagnosed 2.3 million times for the first time, which is 11.7% of all cancer incidence (Shang *et al.*, 2020). Current data shows that one in eight women will develop breast cancer at some point in her lifetime, which underscores the importance of good treatment options (Obeagu *et al.*, 2024) Chemotherapy has for many years been used in the treatment of breast cancer and it is used at various stages of the disease. In early breast cancer, chemotherapy is given before surgery to shrink tumors and with surgery or after surgery to kill remaining cancer cells. It is very important in Triple Negative Breast Cancer (TNBC), a subtype that does not have estrogen, progesterone and HER2 receptors and chemotherapy is one of the rare treatments that are effective for this subtype. Palliative chemotherapy is still the mainstay of care for patients with metastatic breast cancer, to help slow the progression of the disease and improve survival (Jackson *et al.*, 2023).

Some drugs that are used in chemotherapy of breast cancer include Anthracyclines, such as doxorubicin which are very effective but have the tendency of causing cardiotoxicity that leads to long term heart damage. Taxanes such as paclitaxel and docetaxel are very effective but their side effects include neurotoxicity and myelosuppression, which cause nerve damage and low blood cell counts respectively. Platinum-based drugs including cisplatin and carboplatin have shown promising results in TNBC; but their application is usually accompanied by kidney toxicity and other adverse effects (Tian *et al.*, 2023).

Although breast cancer treatments are quite effective, there are two major problems that are associated with the use of these treatments: Systemic toxicity and Drug resistance. Most of the chemotherapy medicines are not target specific and therefore affect both cancer cells and normal cells causing a lot of side effects. However, breast cancer cells are known to develop drug resistance, which means that the long-time treatment is less effective and there is a high chance of the disease returning. The use of breast cancer therapies, however, is still a problem with toxicity of the drugs as well as development of resistance to the drugs. Treatment is a process that cancer cells can learn from, and thus change to become resistant to the therapy. For instance, tamoxifen is used to treat ER^+ breast cancer, but the cancer often becomes resistant to it; trastuzumab is used for HER^{2+} breast cancer but the cancer may become resistant to it. These mechanisms of resistance render the long-term treatment ineffective and lead to recurrence of the disease.

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Another major problem in breast cancer management is low tumor penetration of drugs, which prevents the drugs from killing all cancer cells in the tumor. However, most tumors are solid tumors and have a high-density Extracellular Matrix (ECM) that contains collagen, hyaluronic acid, and fibrous proteins that form a physical barrier to drug delivery. Furthermore, tumors are known to have an abnormal and disorganized vasculature that results in poor drug delivery through the blood stream. This form of blood supply results in hypoxic areas which can enhance the cancer cell survival and render them resistant to the treatment. Structural barriers are also an issue, but there is also the issue of high Interstitial Fluid Pressure (IFP) in the tumor microenvironment that prevents the drugs from moving freely to the tumor. This pressure gradient affects the ability of the systemically administered drugs to penetrate deeper into the tumor, leaving behind cancerous cells that can cause recurrence and metastasis of the tumor. The issue is particularly problematic in aggressive breast cancer subtypes including TNBC where traditional chemotherapy depends on profound tumor penetration to be effective. Furthermore, drug efflux pumps such as P-glycoprotein (P-gp) and Multidrug Resistance (MDR) transporters decrease the accumulation of drugs within tumor cells. These efflux pumps actively remove chemotherapeutic agents from cancer cells before they can exert their cytotoxic effects, thus reducing the efficacy of treatment. The situation is compounded by the fact that both poor drug penetration and efflux pump activity lead to relatively low drug concentrations in the tumor core, thus allowing resistant cancer cells to prosper, proliferate and cause recurrence of the tumor.

One of the biggest problems in breast cancer treatment is metastases, which is the progression of cancer cells from the primary tumor to other parts of the body. Metastatic Breast Cancer (MBC), or stage IV breast cancer, is the advanced cancer of the breast that has spread to other organs such as lungs, liver, bones, and brain and is the leading cause of death from breast cancer (Wang *et al.*, 2019). Despite the improvements in the screening and treatment of early cancer, metastases are virtually impossible to control and current therapy is often aimed at reducing symptoms rather than eradicating the disease. Metastasis is a step-by-step process also referred to as the metastatic cascade, and it begins with local invasion, intravasation (entry into the bloodstream or lymphatic system), circulation, extravasation (exit from blood vessels) and colonization of secondary sites. EM, immune privilege and apoptosis resistance are the biological factors that favor the metastasis of cancer cells. When cancer cells move to other organs, they become more aggressive and are less likely to respond to the usual forms of treatment, making the metastatic disease more difficult to control. An issue that poses a major problem in the treatment of metastatic breast cancer is the spread of cancer cells in circulation and their ability to hide from the immune system. Circulating Tumor Cells (CTCs) also develop adaptive mechanisms that include increasing the surface markers protein such as CD44 and CD47 to avoid being recognized and attacked by the immune system. Also, CAFs, EVs, and exosomes in the tumor microenvironment enable metastasis through angiogenesis, modulation of immune responses, and promotion of tumor cell migration. These factors pose a problem in the development of therapies that can effectively prevent or kill metastatic cancer cells. Another key challenge is organ specific metastasis in which breast cancer cells adhere to certain distant organs based on the availability of the microenvironment. For example, more than 70% of patients with metastatic breast cancer develop bone metastases because the cancer cells secrete osteoclast activating factors that cause destruction of bone, fractures and pain (Tahara *et al.*, 2019). In the same way, brain metastases are hard to treat because of the Blood Brain Barrier (BBB) which is usually resistant to most of the chemotherapy drugs used in treatment. These peculiarities require innovative strategies for the delivery of specific and targeted therapy to improve the quality of life of patients with metastatic breast cancer.

In nutshell, it is crucial to explore new and improved drug delivery systems that can overcome these limitations and render effective therapy with minimal adverse effects. Some of the current challenges include insufficient drug selectivity, adverse effects, and drug resistance. Each of these approaches is discussed in detail below, with an emphasis on their potential to improve the delivery, efficacy, and safety of cancer therapeutics. Given these challenges, there is an urgent need for advanced drug delivery strategies that enhance therapeutic efficacy while minimizing toxicity and overcoming resistance. Emerging approaches such as nanoparticle-based delivery, antibody-drug conjugates, and stimuli-responsive drug carriers hold promise in addressing these limitations by improving drug selectivity, reducing side effects, and bypassing resistance mechanisms. In the context of cancer therapy, the development of advanced drug delivery systems is crucial for improving the precision, efficacy, and safety of current treatment regimens. As healthcare providers strive to optimize patient outcomes while minimizing the impact of chemotherapy on overall health, the integration of innovative drug delivery strategies will play an increasingly important role in the management of cancer.

Nanoparticles-based drug delivery

Nanoparticle based drug delivery is a promising strategy to improve the efficacy and safety of existing breast cancer treatments through greater targeted drug delivery, reduced systemic toxicity and drug resistance. Conventional chemotherapy is associated with numerous limitations, including poor specificity, rapid clearance and severe side effects. Exact site targeted drug delivery, enhanced drug solubility and stability and controlled drug release mechanisms are among the several advantages offered by nanoparticles to improve therapeutic outcomes (Table 1).

Lipid-based nanoparticles

Lipid-based Nanoparticles (LNPs) are currently known nanoparticle systems which have shown potential in breast cancer therapy (Chaudhuri *et al.,* 2022). These nanoparticles, such as liposomes and Solid Lipid Nanoparticles (SLNs), are more biocompatible, have higher drug stability and better tumor accumulation than conventional chemotherapy (Figure 1). Due to the fact that these carriers are lipid-based they can encapsulate both hydrophilic and hydrophobic drugs in order to use for drug delivery applications. The duration of systemic circulation, the reduced off target toxicity and the ability to enhance tumor accumulation of lipid-based NPs via the EPR effect have made this approach promising for enhancing the therapeutic results in patients with breast cancer (Gajbhiye *et al.*, 2023).

Liposomes

Liposomes are phospholipid bilayer vesicles in spherical symmetry and have an ability to incorporate therapeutic agents in their interior or in the bilayer. Liposomes are currently the most widely used nanoparticles in breast cancer therapy, and Doxil, a pegylated liposomal doxorubicin formulation, is the first nanomedicine to be approved by the FDA for cancer treatment. Liposomes are pegylated to make them stealth such that they are cleared by the Mononuclear Phagocyte System (MPS), thereby increasing their plasma half-life (Gabizon *et al.*, 2025). Therefore, liposomal drug carriers are usually accumulated in the tumor tissues due to the EPR effect, which results in higher drug concentrations in the tumor and lower systemic toxicity.

Generally, conventional liposomal systems; however, targeted liposomes have been created to home in breast cancer cells specifically. The receptor-mediated endocytosis and the intracellular drug release are enhanced by functionalization with tumor-targeting ligands, such as HER2 specific antibodies (trastuzumab), folic acid, or transferrin (Alberto *et al.*, 2025). Moreover, liposomes that release their payload in response to pH (Rizwanullah *et al.*, 2021), enzymes or external stimuli (ultrasound, temperature or magnetic fields) are investigated for the controlled drug delivery to the tumor site to enhance the cytotoxic effects with minimal adverse effects (Figure 2) (Zangabad *et al.*, 2018).

Solid Lipid Nanoparticles

Solid Lipid Nanoparticles (SLNs) are another class of lipid-based drug carriers consisting of physiological lipids that are in solid state at the body temperature. These nanoparticles possess the advantages of liposomes and polymeric nanoparticles in that they possess high drug loading capacity, controlled drug release, and are biocompatible (Yoon *et al.*, 2013). SLNs have been investigated for the delivery of chemotherapeutic agents, hormonal therapies and gene-based therapies for the treatment of breast cancer.

The main benefit of SLNs over conventional liposomes is that they are more chemically and physically stable and hence have low drug leakage and degradation. Furthermore, the development of SLN systems is based on the use of natural or synthetic lipids to produce patient friendly biodegradable drug carriers. SLNs have recently been investigated for the delivery of paclitaxel, tamoxifen and curcumin in breast cancer and the formulations revealed enhanced tumor penetration, sustained drug release, and reduced toxicity (Zhou *et al.*, 2024). Moreover, SLNs can be loaded with PEG or targeting ligand modified surfaces to avoid the immune system and increase the site-specific delivery. Recently, the lipid based SLNs have been further improved to generate the lipid-polymer nanoparticles, which are the combination of polymeric nanoparticles with the lipid-based carriers for improving the stability. These hybrid systems have also revealed enhanced cellular internalization, overcome of MDR and better BBB permeation and therefore appear to be promising for the treatment of metastatic breast cancer including brain metastases (Ahmed *et al.*, 2024).

Polymeric Nanoparticles (PNPs)

Polymeric Nanoparticles (PNPs) are currently explored as potential drug carriers for breast cancer treatment owing to their capability to enhance the stability of drugs, control the release of drugs and render site specific delivery of the drugs. These nanoparticles are made of biodegradable and biocompatible polymers including poly (Lactic-co-Glycolic Acid) (PLGA), Polylactic Acid (PLA), chitosan, and Polyethylene Glycol (PEG) that can enhance the loading and tune the release of chemotherapeutic agents. PNP has higher drug loading capacity, increased circulation time and better tumor penetration as compared to conventional drug formulations and thus presents a promising strategy to improve the breast cancer treatment.

A primary advantage of PNPs is the ability to sustain and control the drug release, so that the periods of therapeutic drug concentrations are prolonged. It is especially useful for breast cancer treatment because it reduces fluctuations in drug levels, systemic toxicity and finally improves the overall treatment results. For instance, PLGA nanoparticles degrade with time controlling the drug release and maintaining the prolonged therapeutic effect. This is very important for drugs with short half-life or with dose limiting toxicities like doxorubicin and paclitaxel for which controlled release is essential. One such study evaluated the safety and bioavailability of the developed NPs. The optimized NPs (PDLNPs) achieved a high drug encapsulation efficiency, ensured sustained and controlled drug release, enhanced cellular internalization, and exhibited promising *in vitro* cytotoxicity against MCF-7 and MDA-MB-231 cancer cells (Yildiz *et al.*, 2018). The PEGylation of the NPs improved their stability, circulation time, and targeting efficiency. The co-delivery of paclitaxel and doxorubicin in PDLNPs offered synergistic cytotoxic effects and reduced the requirement for high drug doses, potentially

Table 1: Summarizes the various category and key functions with examples.

Category	Function	Example	Challenges	Future direction
Lipid-Based Nanoparticles.	Improve drug solubility, prolong circulation.	Doxil (liposomal doxorubicin), paclitaxel liposomes.	Rapid clearance, stability issues.	AI-optimized lipid formulations for better targeting.
Polymeric Nanoparticles.	Controlled and sustained drug release.	PLGA NPs, chitosan-based NPs, PEGylated NPs.	Drug loading efficiency, large-scale synthesis.	Smart polymeric designs for stimuli-responsive drug release.
Gold and Magnetic Nanoparticles.	Tumor imaging and drug delivery (theranostics).	Gold nanoshells (photothermal), iron oxide NPs (magnetic-guided).	Non-specific accumulation, toxicity risks.	Surface modifications for tumor-specific binding.
Stimuli-Responsive Nanoparticles.	Triggered drug release in tumor environment.	pH-sensitive NPs, enzyme-activated NPs, heat/magnetic-triggered NPs	Premature release, limited deep tissue penetration.	Premature release, limited deep tissue penetration.
Multidrug Nanocarriers.	Combat Multidrug Resistance (MDR).	Paclitaxel + doxorubicin-loaded NPs.	Drug interaction issues, stability in circulation.	Personalized nanocarriers based on tumor genetic profiling.
RNA-Based Nanoparticles.	Gene silencing to overcome drug resistance.	siRNA/miRNA-loaded NPs, lipid-RNA complexes.	RNA degradation, immune activation	Engineered exosome-mimicking carriers for safe RNA delivery.
Exosome-Based Nanoparticles.	Natural vesicle-based drug transport	Engineered exosomes carrying chemo/RNA drugs.	Large-scale production, purification challenges.	Biodegradable synthetic exosomes for precision therapy.

leading to improved treatment outcomes with reduced systemic toxicity. These results suggest that PDLNPs represent a promising nanotechnology-based platform for the personalized therapy of breast cancer.

Gold and magnetic NPs

Both gold and magnetic nanoparticles are currently investigated for breast cancer diagnosis and treatment because of their dual role in tumor imaging and drug delivery in the concept of theranostics. These nanocarriers allow diagnosis and treatment to be performed simultaneously, thus facilitating the observation of the distribution of the drug and improving the therapeutic index. When engineered to the appropriate size and coated to prevent aggregation and interaction with cells, these NPs exhibit promising physicochemical properties of surface plasmon resonance (gold NPs) and superparamagnetism (magnetic NPs) for effective targeted imaging, controlled drug release, and minimal invasive therapy.

Gold Nanoparticles (AuNPs) are most commonly employed because of their biocompatibility, ease of functionalization, and photothermal properties. AuNPs act by absorbing Near Infrared (NIR) light and producing localized heat to kill cancer cells with minimal impact on normal tissues in PTT (photothermal therapy). Also, AuNPs can be attached to targeting ligands (antibodies, peptides, folic acid) to increase the selective accumulation in the tumor, which can be used for CT and photoacoustic imaging (Goddard *et al.*, 2020). AuNPs also enhance the delivery of chemotherapeutic agents including doxorubicin or paclitaxel to the tumor (Zenjanab *et al.*, 2024), leading to controlled drug release and better treatment results. Magnetic Nanoparticles (MNPs), especially Iron Oxide nanoparticles (Fe_3O_4) improve the effectiveness of breast cancer theranostics through MRI contrast enhancement and Magnetic Hyperthermia Therapy (MHT) (Vangijzegem *et al.*, 2019). These nanoparticles can be steered to the tumor site by an external magnetic field, which leads to higher specificity of drug delivery and thus reduced side effects. Furthermore, these particles when exposed to an alternating magnetic field produce heat, which leads to tumor cell apoptosis while causing almost no harm to the surrounding tissues. The chemotherapy or gene therapy integrated with MNPs increases the therapeutic efficacy of the particles and enhances the potential of synergy in cancer treatment.

Research gap in NPs-based theranostics in breast cancer

Although there are many problems in the application of gold and NPs in the treatment and diagnosis of breast cancer, there are several critical research gaps that have limited their clinical

application. These challenges must be met and overcome to enhance the effectiveness, safety, and manufacturability of the nanoparticle-based drugs and imaging agents.

A major drawback of nanoparticle-based drug delivery systems is the nonspecific accumulation of the nanoparticles in the liver and kidneys, which results in a decreased delivery of the drug to the tumor. The Mononuclear Phagocyte System (MPS), sequesters from the circulation, especially in the liver and spleen, which reduces the efficacy of the nanoparticles (Lu *et al.*, 2023). Current studies are focusing on increasing the tumor recognition and avoiding the liver and kidney uptake through PEGylation of the surface, optimal particle size (50-200 nm) and biomimetic coatings including cell membrane camouflage. More studies are required to design nanoparticles that can avoid the liver and kidney and at the same time have high accumulation in the tumor through targeted delivery and drug release upon stimulation.

Another major problem is the immune system's recognition and removal of nanoparticles from the blood which decreases the time of nanoparticles circulation and the level of their accumulation in the organism. The body sees foreign nanoparticles as dangers and removes them quickly by macrophages and activates complement system. PEGylation has been found to be effective in preventing opsonization, but the use of PEG for a prolonged period may result in ABC (Accelerated Blood Clearance) syndrome in which the particles are recognized by the immune system (El Sayed *et al.*, 2020). Recent approaches include zwitterionic coating, macrophage mimic nanoparticles, and stealth immunorejection for increasing the nanoparticle duration in circulation and their delivery to the tumor (Jia *et al.*, 2025). The move from the laboratory scale synthesis to the industrial level production is still a major problem in the use of gold and magnetic nanoparticles in clinical practice. Present synthesis methods are often slow, labor intensive and the processes are less reproducible which makes the production costly. It is, therefore, important to develop environmentally friendly, scalable, and reproducible synthesis methods in order to make these nanoparticles suitable for widespread clinical use. Microfluidic based synthesis, green chemistry, and automated high throughput production are currently being investigated to address these problems (Hessel *et al.*, 2022). Also, nanoparticle-based therapies need to be evaluated for quality control, safety and long-term biocompatibility, thus highlighting the need for well-defined production methods.

Tumor targeting strategies

Antibody Drug Conjugates (ADCs)

Antibody-Drug Conjugates (ADCs) are a sophisticated therapeutic strategy for targeted breast cancer treatment, which links the selectivity of the monoclonal Antibodies (mAbs) to the cytotoxic power of small molecule drugs (Ponziani *et al.*, 2020). The concept of ADC is to target the chemotherapeutic agents to the cancer cells through the expression of specific tumor associated antigens, thereby reducing the off-target toxicity and improving the therapeutic index. ADCs are currently in use for the treatment of breast cancer, particularly HER2 positive and Triple Negative Breast Cancer (TNBC), with many more under clinical investigation.

ADCs are composed of a monoclonal Antibody (mAb), a cytotoxic payload, and a linker that attaches the drug to the antibody. The antibody targets a specific Tumor-Associated Antigen (TAAs), such as HER2 or Trop-2, thereby increasing the specificity of the delivery. After the ADC is internalized by receptor-mediated endocytosis, the cytotoxic drug is released into the cancer cell, inducing apoptosis. This high-selectivity mechanism improves the therapeutic index over conventional chemotherapy by reducing systemic toxicity. ADCs have recently been approved for the treatment of breast cancer and have led to better patient

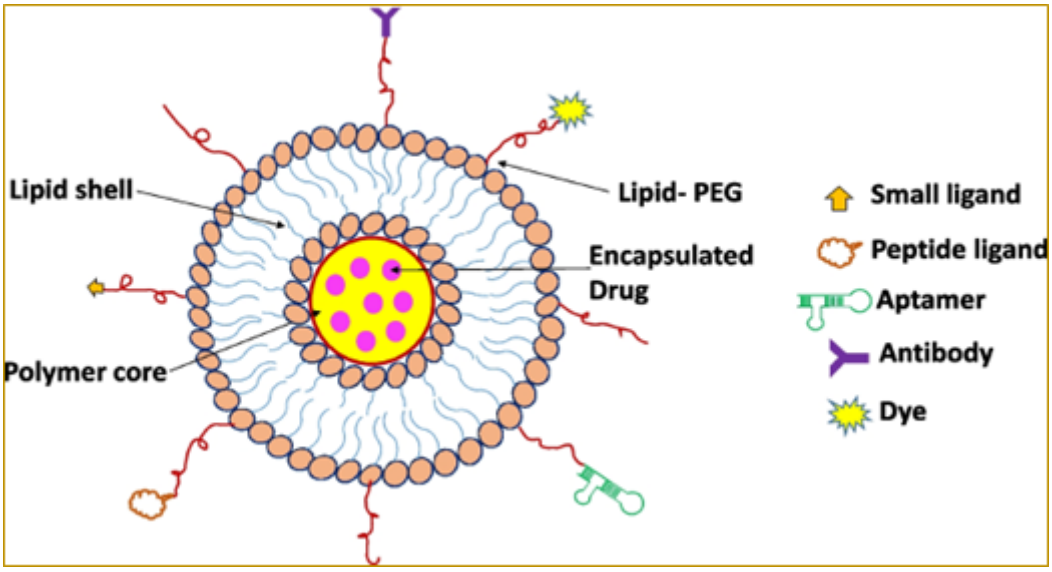

Figure 1: Lipid polymer hybrid nanoparticles; structural components and various possible functionalities.[8]

results (Saini *et al.*, 2024). T-DM1, Kadcyla® is one of the first ADCs to treat HER2 positive breast cancer with trastuzumab and DM1, a microtubule inhibitor. Trastuzumab deruxtecan (Enhertu®), recently approved, has better efficacy because of its more favorable drug to antibody ratio and better linker stability (Díaz-Rodríguez *et al.*, 2021). Sacituzumab govitecan (Trodelvy®) has become a breakthrough therapy for TNBC, which delivers SN-38, a potent topoisomerase I inhibitor, to Trop-2 expressing tumors (Guerra *et al.*, 2022).

Peptide-Drug Conjugates (PDCs)

Peptide-Drug Conjugate (PDC) is a new type of targeted cancer therapy that uses tumor-seeking peptides to transport cytotoxic drugs to cancer cells. As opposed to ADCs, PDCs have several benefits, including a smaller size that improves the penetration of tumors, lower immunogenicity, and a relatively inexpensive synthesis. Because of these features, PDCs are very attractive for the treatment of breast cancer where the problem of effective targeted delivery of drugs is still critical. The structure of a PDC usually comprises three elements: a targeting peptide, a cytotoxic drug, and a linker that regulates the drug delivery (Fu *et al.*, 2023; Xu *et al.*, 2022). Peptides are engineered to interact with tumor-related antigens, such as HER2, EGFR, integrins (among them αvβ3) or GRP78 that are amplified on the surface of breast cancer cells (Ma *et al.*, 2023). When it comes to binding, PDC is internalized into the cell via receptor-mediated endocytosis and then the drug is released into the cell to kill the cancer cell specifically. This specific delivery system prevents systemic toxicity and decreases the side effects of conventional chemotherapy since the rest of the healthy cells are less likely to be affected. Various PDCs are currently being explored for breast cancer therapy with encouraging preclinical and clinical results. The most common strategy is to use RGD-based peptides that are expressed at high levels in the most aggressive breast cancer subtypes such as TNBC (Javid *et al.*, 2024). Furthermore, the conjugation of cytotoxic agents to HER2-targeting peptides has been found to be highly selective and tumor inhibitory, potentially representing a non-antibody-based alternative (Deonarain *et al.*, 2021). Some PDCs further apply dual-targeting, where one peptide recognizes several antigens to increase the tissue selectivity and to circumvent the mechanisms of resistance (Sui *et al.,* 2023).

Aptamer-based targeting

Aptamer-based targeting is coming up as a potential approach in breast cancer therapy, which uses RNA and DNA aptamers with their high specificity and affinity to target tumor biomarkers. Aptamers are brief structured oligonucleotides that can interact with particular proteins, receptors or even small molecules on the cancer cells with high accuracy (Ruiz Ciancio *et al.,* 2018). Aptamers differ from the monoclonal antibodies; they are small, immune to generate allergic reactions, easy to synthesize, and very stable and, therefore, suitable for application in targeted drug delivery, imaging and therapy. There are number of biomarkers like HER2, EpCAM, MUC1, VEGF, and nucleolin that are overexpressed in various breast cancer subtypes that can be targeted by the aptamers in breast cancer. HER2 specific aptamers that have been developed to recognize HER2 positive breast cancer cells are an alternative to trastuzumab monoclonal antibodies (Jeong *et al.*, 2020). In the same manner, VEGF aptamers can block angiogenesis thus denying the cancer cells the necessary blood supply for growth and metastasis (Ghasemali *et al.*, 2021). Some of the aptamers are ApDCs (aptamer drug conjugates), where a toxic compound is linked to the aptamer such that the ApDCs target the cancer cells selectively with minimal effects on the rest of the body (Park *et al.*, 2024; Cao 2023). Another promising aptamer application is in diagnostics and imaging that uses fluorescent or radio-labeled aptamers for real time tumor imaging to help in the detection of cancer and to monitor the treatment outcomes (Ashique *et al.*, 2023). Aptamers are integrated into biosensors and liquid biopsy devices to detect circulating tumor markers from patient blood samples with high sensitivity.

Research gap

Although RNA/DNA aptamers have considerable potential as therapeutic agents in breast cancer, there are several problems that have to be solved to enhance their effectiveness. The research gaps in this area are primarily related to improving the mechanisms of drug delivery, overcoming the resistance to treatment due to receptor downregulation, and ensuring the safety of the linker chemistry in the ApDCs. These issues are important to further develop aptamer-based technologies from the laboratory to the clinic.

The major drawback of ApDCs is the controlled and efficient delivery of the drug after the aptamer has attached to the tumor target. Most of the current systems have problems with early drug release in the circulation or poor release inside cancer cells, which leads to reduced therapeutic response. To solve this problem, stimulus-sensitive linkers can be used that can be made to release the drug in the presence of certain tumor microenvironment stimuli, such as low pH, enzymes, or redox potential. Further study is required to design better and more accurate and controllable drug release systems that can maximize the delivery of drugs to cancer cells with minimum impact on the whole body. The problem of aptamer-based therapy is the development of resistance of breast cancer cells to aptamers due to the downregulation or mutation of the receptors attached to the aptamers. This phenomenon has been noticed with antibody-based therapies such as trastuzumab in HER2-positive breast cancer and may occur with aptamer-based treatments as well. To this end, biparatopic aptamers or biparatopic aptamer constructs have been proposed to engage two tumor-associated receptors simultaneously. However, aptamers delivering RNAi agents or CRISPR-based gene editing may also be useful to

decrease the expression of the target receptor on the tumor cell surface, thus reducing the efficacy of the aptamers.

The linker moiety in ApDCs is crucial in determining the stability of the drug, its controlled release, and the overall toxicity of the complex. Some of the current linkers are based on chemical moieties that may be toxic or unstable *in vivo* and may therefore cause adverse effects or decomposition leading to unwanted reactions. At present, biodegradable and non-toxic linkers, including disulfide bonds, enzyme-cleavable peptides, and acid labile linkers, are being investigated to improve the aptamer-based drug delivery system with higher specificity. More research is still needed to design linkers that are stable in the circulation but can release the drug effectively inside the cell to improve the therapeutic results.

Stimuli-responsive drug delivery

pH-sensitive NPs

Stimuli-responsive drug delivery systems based on pH-sensitive nanoparticles have been explored to administer drugs based on the acidic microenvironment of tumors. Tumors are generally found to have lower extracellular pH (6.2-6.9) than the normal physiological pH (7.4) due to factors such as anaerobic metabolism and poor perfusion (Peppicelli *et al.*, 2024). This acidity along with the more acidity of intracellular compartments like endosomes (pH 5.5-6.0) and lysosomes (pH 4.5-5.5) offers an excellent opportunity to develop NPs that can alter the structure and hence drug release in the tumor or cancer cells in response to the pH (Ahmad *et al.*, 2024). The NPs are stable in circulation and degrade or show structural changes in the acidic environment, thus ensuring that drugs are released only at the target site with minimal side effects and toxicity (Desai *et al.*, 2024). The pH-sensitive NPs have several mechanisms that have been identified to mediate the targeted drug delivery in response to acidity. The most common mechanism is the protonation induced charge conversion, where the NPs are negatively charged in the physiological pH and turn positively charged in the acidic pH. This alteration in the charge enables the binding of the NPs to the negatively charged cancer cell membranes and thus increases the internalization (Sethuraman *et al.*, 2021). Another mechanism is based on the use of acid labile linkers, such as hydrazone, imine or ester bonds that are incorporated to break down under the acidic conditions of the tumor or cancer cell to release the drug at the right location (Mishra *et al.*, 2023). Furthermore, polymeric NPs prepared from pH sensitive materials can rotate, burst, or degrade in the acidic milieus to achieve the controlled delivery of the incorporated drugs (Beach *et al.*, 2024). The chief benefit of applying pH-sensitive NPs in cancer treatment is that they can control the drug delivery to the tumor, thus preventing the concentration of the drugs in other organs. This is particularly important in the context of MDR, since the pH of endosomes and lysosomes is also low and may not allow the functioning of efflux pumps that are normally resistant to conventional chemotherapeutic agents such as doxorubicin and paclitaxel. Furthermore, pH-sensitive NPs can improve the cellular uptake as the pH gradient leads to the charge switch over, which helps in better penetration and retention in the tumor tissues. These nanoparticles also provide the opportunity of simultaneous delivery of chemotherapy, gene therapy or immunotherapeutics for combination therapy (Li *et al.*, 2020).

In cancerous tissues, enzyme overexpression or dysregulation is well known to play a critical role in tumor progression, invasion and metastasis (Shi *et al.*, 2024). The enzymatic differences

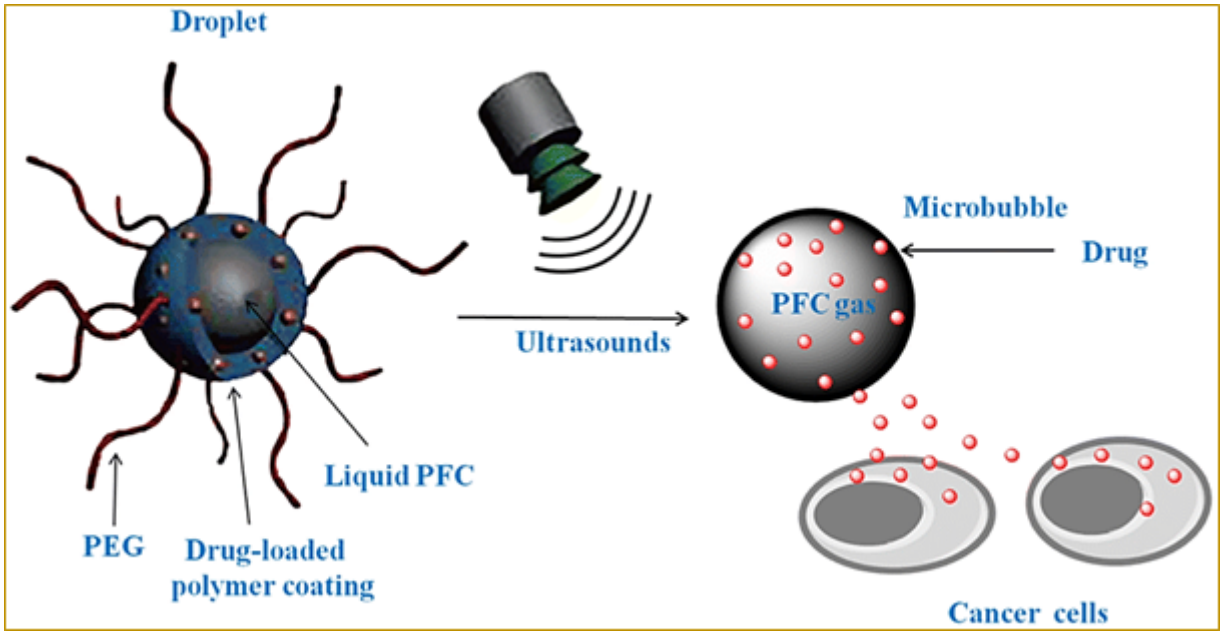

Figure 2: Ultrasound responsive nanodrug delivery system.[54]

between healthy and malignant tissues have encouraged the development of intelligent drug carriers that are inactive in circulation and activated only at the tumor site. Enzyme activated systems improve drug accumulation in tumors, reduce systemic toxicity and circumvent drawbacks such as poor drug penetration and MDR, which are Inefficient in conventional chemotherapy. The general principle of enzyme activated drug delivery is based on enzyme cleavable linkers or biodegradable nanocarriers that are degraded by enzymatic activity specifically enriched in the tumor microenvironment. Protease responsive drug carriers are one of the best studied strategies, where tumor associated proteases, including matrix metalloproteinases, cathepsins, and urokinase type Plasminogen Activator (uPA) can cut peptide-based linkers to trigger drug release (Chaturvedi *et al.*, 2024). Proteases involved in these include MMPs (matrix metalloproteinases) which are involved in Extracellular Matrix (ECM) degradation to facilitate tumor invasion, and their selective targeting enhances drug penetration in solid tumors (Henke *et al.*, 2020). Another category is glycosidase activated systems, where enzymes like β-glucuronidase and hyaluronidase, that are overexpressed in tumors, degrade polysaccharide-based drug carriers or glycosidic linkers to control drug release (Shahriari *et al.*, 2019). This approach is especially useful for tumors rich in hyaluronic acid, like TNBC, where nanoparticles sensitive to hyaluronidase can enhance the delivery of drugs. Both phosphatase- and kinase-responsive systems show growing interest in addition to protease- and glycosidase-based activation. These enzymes function significantly in cell communication systems and cancer cell energy production making them important targets for drug activation. Systemic circulation enables alkaline phosphatase responsive prodrugs to remain inactive until they get enzymatically activated within the tumor environment. The local drug delivery system delivers therapeutic agents only to cancerous tissues which avoids harming healthy cells and reduces chemotherapy-induced toxicity. The principal benefit of enzyme-activated drug delivery systems consists of targeted tumor activation which delivers therapeutic agents only to cancer cells while minimizing systemic toxicity and side effects. These systems improve tumor penetration because enzyme-driven degradation of ECM components facilitates greater drug diffusion across solid tumors while surpassing traditional chemotherapy restrictions. Drug-loaded platforms that utilize enzyme activation overcome MDR mechanisms because drug activity inside cells blocks efflux pumps resulting in enhanced treatment effectiveness. Enzyme-activated carriers deliver drugs through a controlled and sustained delivery pattern which reduces patient medication frequency and enhances patient adherence to treatment.

Photothermal and magnetic triggered release

Stimuli-responsive drug delivery systems that employ photothermal and magnetic-triggered release have received much attention in cancer therapy due to their ability to control the release of drugs both spatially and temporally (Jose *et al.*, 2021). These approaches generally use external stimuli, such as near-infrared light or magnetic fields, to targeted activate drugs at the tumor site to reduce systemic toxicity and improve therapeutic efficacy. These strategies combine heat-responsive nanomaterials or magnetically sensitive carriers to non-invasively control drug release with externally controllable magnetic fields, which presents a promising new alternative to conventional chemotherapy.

The concept of photothermal-triggered drug release depends on the use of photothermal agents such as Gold Nanoparticles (AuNPs), Graphene Oxide (GO), Carbon Nanotubes (CNTs), and Metal Organic Frameworks (MOFs) which can effectively absorb the near-infrared light (700-1100 nm) and transform it into heat (Manivasagan *et al.*, 2022). This heat can bring about phase transitions, or break chemical bonds or increase membrane permeability for drug delivery at the tumor site. Further, photothermal materials can produce localized hyperthermia that can help in drug delivery, destroy tumor vasculature, and kill cancer cells, which makes it a dual therapeutic approach highly effective. This method is especially beneficial for solid tumors like TNBC as it is difficult for deep tumor penetration and control of drug release can greatly improve the treatment response.

The magnetic-triggered release system depends on superparamagnetic nanoparticles (e.g., Iron Oxide NPs, Fe_3O_4) which are triggered by externally applied Alternating Magnetic Fields (AMFs) (Orsi *et al.,* 2023). The nanoparticles produce localized heat or mechanical force when exposed to AMFs, which causes on-demand drug release through the disruption of nanoparticle coatings or structural changes in drug carriers. External static magnetic fields direct drug-loaded magnetic nanoparticles to the tumor site in magnetically guided drug delivery systems, which improves drug accumulation while reducing off-target effects. Because conventional drug delivery methods frequently exhibit poor penetration and non-specific distribution to deep-seated tumors, this approach becomes particularly beneficial for these conditions. The local control of drug delivery is achieved through photothermal and magnetic-triggered systems which provide high precision in both space and time to activate drug release only at tumor locations while reducing potential harmful effects on surrounding healthy tissues. Because these methods can be repeated or adjusted in real time, they are very applicable to personalized treatment strategies. Theranostics applications of both photothermal and magnetic-responsive nanoparticles are possible because they can be engineered to combine tumor imaging (MRI, photoacoustic imaging) with therapy while monitoring treatment response in real time (Farjadian *et al.*, 2022; Wang *et al.*, 2023).

Research gaps

The majority of stimulus-responsive carriers show leakage as a result of labile chemical bonds and low trigger selectivity, resulting in drug release in incorrect locations and, therefore, reduced therapeutic effectiveness. In order to solve this problem, scientists need to design more long-circulating nanocarriers that can be activated only at the tumor site by tumor-related stimuli like pH, enzymes or heat. Furthermore, the development of multi-stimuli responsive systems that require the presence of multiple tumor specific triggers may provide greater specificity and reduced risk of premature drug activation (Zhang *et al*., 2024).

Stimuli-responsive drug delivery systems present another important issue that needs to be addressed which is tissue damage. External stimuli including photothermal and magnetic fields allow drug release in space, but nearby normal tissues may suffer thermal damage or unintended toxicity during the process. As a proof of concept, photothermal therapy produces localized heat but uncontrolled heat delivery can cause hyperthermic injury to healthy cells. For instance, enzyme-activated systems might lead to non-specific activation because the targeted enzymes may also be present in non-cancerous tissues. This means that researchers have to improve dosage optimization, spatial resolution and heat dissipation control in photothermal-based therapies. Furthermore, the use of tumor-selective nanoparticles with targeting ligands may also help in minimizing non-specific interactions and thus enhance the safety and efficacy of delivery. The other major issue that needs to be addressed is the problem of tissue penetration which is still an issue for photothermal drug delivery systems that are activated by near-infrared light. While near-infrared light has the ability to penetrate more deeply into tissues than visible light its effectiveness drops off dramatically in deep-seated tumors and thus is only effective for treating superficial or subcutaneous cancers. To enhance penetration, researchers are using two-photon excitation techniques, up conversion nanoparticles, and higher efficiency NIR absorbers to deliver more light energy into deeper tissues (Du *et al.*, 2024). Furthermore, using magnetic responsive carriers combined with photothermal agents can provide dual-stimuli responsive drug delivery to enhance the delivery of drugs to deep tumors.

Overcoming drug resistance

Multidrug nanocarriers- overcoming chemotherapy resistance

Breast cancer treatment is a major problem because one of the biggest problems is drug resistance. Such as the overproduction of efflux proteins like P-glycoprotein, activation of cell survival pathways by proteins like PI3K/Akt and NF-κB, and changes in drug targets, cancer cells are able to resist the cell death that is induced by chemotherapy (Dhanyamraju *et al.*, 2024). Multidrug nanocarriers are now recognized as potential strategies to deliver drug combinations that can prevent or at least delay the onset of resistance (Imran *et al.*, 2022).

Tumor-targeting nanocarriers are engineered nanoparticles which are able to carry multiple chemotherapy drugs in one platform, releasing one or more drugs simultaneously or in sequence at the required location. The delivery of drugs via these nanocarriers that work differently can improve treatment effectiveness without increasing the chance of drug resistance. Thus, lipid-based NPs and PCL-based polymeric NPs have been developed to deliver paclitaxel and doxorubicin which are frequently used in breast cancer treatment. It means that two drugs act on different cellular pathways which increase the probability of complete tumor destruction. Co-delivery of chemotherapy with resistance-modulating agents is another strategy (Bulkurcuoğlu *et al.*, 2024). For example, multidrug nanocarriers containing doxorubicin and verapamil (P-glycoprotein inhibitor) be used to block drug efflux, which results in enhanced drug accumulation in the intracellular space of resistant breast cancer cells (Patel *et al.*, 2024; Kumari *et al.*, 2023). In addition, nanoparticles that carry paclitaxel together with PI3K/Akt inhibitors can block survival pathways that are known to contribute to chemoresistance in TNBC (Engle *et al.*, 2022).

Another advantage of multidrug nanocarriers besides improving efficacy is that they have several advantages over conventional drug delivery systems, including the prolonged circulation time, tumor-specific targeting, controlled drug release, and reduced systemic toxicity. Moreover, tumor targeted drug delivery by the pH sensitive or enzyme responsive nanoparticles further advances the delivery systems to have almost no side effects.

RNA-based co-therapies-silencing resistance mechanisms

Breast cancer cells develop resistance to chemotherapy by acquiring genetic and molecular modifications which enable them to survive drug-induced cell death. The resistance mechanisms are diverse and include; increased expression of drug efflux proteins (for instance P-glycoprotein), stimulation of cell survival pathways (such as PI3K/Akt, NF-κB), apoptosis suppression (for instance via Bcl-2 overexpression) and increased DNA repair. A promising way to tackle such resistance mechanisms is through the application of RNA based co-therapies, which are based on small interfering RNA (siRNA) or microRNA (miRNA) that can specifically target genes linked to drug resistance.

siRNA-based therapies

The use of siRNA molecules represents a potential strategy to design targets that can destroy the mRNA of genes linked to chemotherapy resistance in order to prevent the expression of resistance-related proteins. For instance, siRNA that targets the ABCB1 gene (P-glycoprotein), an efflux pump that removes chemotherapeutic agents from cancer cells, has been shown to bring back sensitivity to drugs like doxorubicin and paclitaxel (Patel *et al.*, 2024). Thus, siRNA that knocks down Bcl-2, an

anti-apoptotic protein, can overcome chemoresistance in TNBC by promoting apoptosis after drug exposure (Samia *et al.,* 2024).

miRNA-Based Therapies

In the case of breast cancer, miRNAs are small non-coding RNAs that act as gene expression regulators by binding to the mRNA transcripts and preventing their translation. Some of them are tumor suppressors while others are oncogenes; thus, they are potential therapeutic targets in breast cancer. For instance, miR-34a has been demonstrated to inhibit the PI3K/Akt pathway that is a crucial survival pathway in HER2+ and TNBC subtypes of breast cancer (Abu-Alghayth *et al.*, 2024). MiR-34a+ breast cancer cells that are resistant to treatment have their proliferation reduced and apoptosis increased upon restoration of miR-34a expression. Other agents such as miR-200c that control the EMT also provide potential ways of preventing drug resistance and reducing the incidence of metastasis in aggressive breast cancer (Ahmadi-Hadad *et al.*, 2024).

Nanoparticle Delivery for RNA Therapeutics

RNA therapy faces an important challenge related to the short circulation time because enzymes in blood fluids rapidly break down RNA molecules. To address this issue, nanoparticle-based delivery systems, including LNPs, polymeric nanoparticles and exosomes have been created for the protection of RNA molecules, targeted delivery to tumour cells and uptake by cells. More specifically, LNPs have gained prominence as they have been utilized in mRNA vaccine technology and thus are shown to be effective in therapeutic RNA delivery in cancer therapy.

Exosome-based drug delivery-a biocompatible approach

The use of breast cancer chemotherapy resistance by cells means a big problem that exosome delivery systems aim to solve by using natural extracellular vesicles that carry drugs in efficient and bio-compatible ways. Exosomes are 30-150 nm vesicles which various cell types produce to communicate with one another through the transfer of proteins, lipids, and nucleic acids. Due to their natural origin, low immunogenicity, and the ability to cross biological barriers, exosomes emerge as a better option as compared to synthetic drug delivery systems. Exosomes in breast cancer therapy are designed to deliver chemotherapeutic agents, siRNA, miRNA, and targeted therapies to enhance the drug accumulation at the tumor site and reduce systemic toxicity (Zhang *et al.*, 2023). The ability to use exosomes is that they are biocompatible and have a prolonged circulation time. Due to the natural origin of exosomes, they do not elicit an immune response and have a longer half-life, which results in better tumor uptake compared to synthetic nanoparticles. Moreover, exosomes can be made to home in on breast cancer cells more effectively. For example, trastuzumab or lapatinib loaded on exosomes bearing HER2-specific ligands can target HER2-positive breast cancer cells, which increases the delivery of these drugs to the intended cells (Mercogliano *et al.*, 2023). This approach not only enhances the therapeutic effectiveness but also decreases the side effects that are not related to the intended target cells and, therefore, reduces the damage to the healthy tissues.

Exosome-based drug delivery systems represent a crucial advancement for treating breast cancer by enhancing the delivery and efficacy of chemotherapeutic agents. The application of exosome-based delivery for the incorporation of chemotherapeutic agents to improve their solubility and delivery into cancer cells represents another important clinical use. Research has shown that exosomes associated with paclitaxel or doxorubicin show enhanced cytotoxicity to TNBC cells compared to conventional free drug delivery systems indicating their potential to increase drug effectiveness. Exosomes have the capability to deliver several types of therapeutic agents at once, such as a chemotherapy medication and a resistance-modulating RNA therapy, to address multidrug resistance. For instance, exosomes loaded with doxorubicin together with siRNA against ABCB1 (P-glycoprotein) have been shown to deliver effective drug accumulation into resistant breast cancer models while restoring their sensitivity to chemotherapy (Guo *et al.*, 2024). Exosomes function as gene delivery vehicles to transmit RNA therapies in addition to their role in chemotherapeutic drug delivery. Breast cancer resistance occurs through two main mechanisms: activation of survival pathways such as PI3K/Akt and NF-κB, and increased expression of anti-apoptotic proteins including Bcl-2. Research has investigated the use of exosomes to deliver miRNAs (e.g., miR-34a, miR-200c) and siRNA targeting resistance-related genes to counteract these mechanisms. Exosome-delivered RNA therapies that silence oncogenic pathways enhance chemotherapy effectiveness while preventing tumor relapse.

Research gaps

There are several research gaps that must be addressed in order to optimize the effectiveness of exosome-based drug delivery in breast cancer therapy. A major issue is how to increase the stability of RNA in plasma. siRNA and miRNA are among the class of molecules that are most vulnerable to the action of ribonucleases in blood. Although the use of exosomes can provide some shield to the RNA, other approaches, including chemical stabilization of the RNA or the use of lipids may be required to extend the half-life of the RNA and thus enhance delivery. Another major issue is to prevent off-target gene silencing effects. The principle of siRNA and miRNA therapy is to target specific mRNA sequences but the possibility of binding to off-target genes is a major concern that can result in unwanted side effects or interference with normal cell functions. To this end, researchers are still working on sequence optimization, better bioinformatics tools for target identification and exosome surface modification to increase tumor uptake. Modification of exosomes to carry breast cancer receptor-like ligands or the use of exosomes that release their content at acidic

pH may also help in targeting the delivery of RNA to the tumor cells more accurately.

The major limitation in the application of exosome-based therapies in the clinic is the lack of efficiency in exosome purification and scalability. The existing procedures include ultracentrifugation and size-exclusion chromatography, which are tedious and produce low yields, thus rendering them unsuitable for large-scale production. A new standardized, high-yield isolation methods such as microfluidic-based separation or large bioreactors will be crucial for the commercial feasibility and clinical implementation of exosomes. Furthermore, another problem that has not been fully addressed is the batch-to-batch variation in exosome purity, cargo capacity, and bioactivity.

Future direction

The field of nanoparticle-based drug delivery experiences rapid development while several cutting-edge approaches show potential to improve treatment precision and efficacy in breast cancer therapy. The future treatment advancements will emerge from AI-guided drug design together with personalized medicine and hybrid therapeutic systems which show the ability to address existing challenges in drug resistance and tumor targeting as well as treatment durability. AI-guided drug design represents an exciting development because it utilizes machine learning algorithms with computational models to predict ideal nanoparticle formulations together with drug combinations and targeting ligands (Yingngam *et al.*, 2024). AI analyses extensive datasets about tumor biology alongside drug interactions and nanoparticle behaviour to design nanocarriers which demonstrate both high specificity and efficiency and biocompatibility. This method cuts down both time and expense from standard experimental procedures and enables quick development of customized drug delivery systems for various breast cancer subtypes. Personalized medicine represents a transformative approach because it develops customized drug delivery methods that match a patient's tumor genetic information along with their molecular profiles. Breast cancer demonstrates substantial variation as HER2-positive and ER-positive conditions differ from TNBC which require unique treatment solutions. Modern advances in genomic sequencing together with biomarker identification enable the creation of personalized nanoparticle-based drug formulations for individual patients leading to effective treatment with reduced side effects. Research shows that RNA-loaded nanoparticles can be programmed to inhibit genes which cause tumor resistance thus enhancing chemotherapy effectiveness. Hybrid therapeutic systems show promise as a treatment approach which combines drug delivery with immunotherapy for enduring patient success (Chung *et al.*, 2002). Current treatment methods including conventional chemotherapy and precision medicine face obstacles because tumors develop resistance to these therapies. The integration of nanoparticle-based drug carriers with immune checkpoint inhibitors together with cancer vaccines and engineered immune cells represents a new treatment strategy that aims to create combined therapeutic effects to destroy tumor cells while activating the body's natural defense system against future cancer growth. The recent medical breakthrough shows great importance for aggressive and drug-resistant breast cancer subtypes since it addresses the difficulty of maintaining durable treatment responses. The ongoing development of these innovations will position AI-driven design together with personalized nanomedicine and immunotherapy-based hybrid systems as essential components to create new breast cancer treatment approaches which deliver patient-specific treatment with longer therapy periods.

CONCLUSION

Targeted delivery of small molecules in breast cancer has been shown to be a significant improvement in the delivery of treatment, which can reduce the systemic toxicity and drug resistance. Some of the recent strategies include use of nanoparticle-based carriers, Antibody Drug Conjugates (ADCs), Peptide Drug Conjugates (PDCs) and exosome delivery systems that can increase the drug delivery to the tumor with minimal side effects. Some of the recent advances include stimulus sensitive systems, RNA based co-therapies and AI guided drug design to further improve the delivery efficiency and the therapeutic results. As long as research keeps on trying to solve the problems of tumor penetration, immune evasion, and large-scale production of the nanoparticles then these innovations may be the key to changing breast cancer therapy to a better and more personal approach.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ABBREVIATIONS

WHO: World Health Organization; **TNBC:** Triple negative breast cancer; **ECM:** Extracellular matrix; **IFP:** Interstitial fluid pressure; **P-gp:** P-glycoprotein; **MDR:** Multidrug resistance; **MBC:** Metastatic breast cancer; **CTCs:** Circulating tumor cells; **BBB:** Blood brain barrier; **LNPs:** Lipid-based nanoparticles; **SLNs:** Solid lipid nanoparticles; **PNPs:** Polymeric nanoparticles; **AuNPs:** Gold nanoparticles; **GO:** Graphene oxide; **CNTs:** Carbon nanotubes; **MOFs:** Metal organic frameworks; **AMFs:** Alternating magnetic fields; **siRNA:** Small interfering RNA; **miRNA:** microRNA; **ADCs:** Antibody drug conjugates; **PDCs:** Peptide drug conjugates.

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