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Nanoparticle-Based Drug Delivery Systems and Targeting Strategies in Breast Cancer Therapy

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Abstract

Breast cancer continues to be a major contributor to cancer-related mortality globally, highlighting the critical importance of developing more efficient and safer therapy strategies. Nanoparticle-based drug delivery systems offer a promising approach by enhancing drug accumulation in tumor tissues while minimizing systemic toxicity. This article explores the unique properties and advantages of various nanoparticles, including liposomal, polymer-, metal-, carbon- and mesoporous silica nanoparticles, in breast cancer therapy. Additionally, it delves into three key targeting mechanisms: passive targeting via the enhanced permeability and retention (EPR) effect, active targeting using ligands and antibodies, and stimuli-responsive drug delivery systems. Integrating nanotechnology into breast cancer therapy paves the way for more precise, efficient, and personalized therapy options, offering new hope for improved patient outcomes.

Keywords: Breast Cancer, Drug Delivery Systems, Nanoparticle

Meme Kanseri Tedavisinde Nanopartikül Tabanlı İlaç Taşıma Sistemleri ve Hedefleme Stratejileri

Özet

Meme kanseri, dünya genelinde kansere bağlı ölümlerde önemli bir rol oynamaya devam etmekte olup, daha etkili ve daha güvenli tedavi stratejileri geliştirmenin kritik önemini vurgulamaktadır. Nanopartikül bazlı ilaç dağıtım sistemleri, sistemik toksisiteyi en aza indirirken tümör dokularında ilaç birikimini artırarak umut verici bir yaklaşım sunmaktadır. Bu makale, meme kanseri tedavisinde lipozomal, polimer, metal, karbon ve mezogözenekli silika nanopartiküller de dahil olmak üzere çeşitli nanopartiküllerin benzersiz özelliklerini ve avantajlarını araştırmaktadır. Ayrıca, üç temel hedefleme mekanizması üzerinde durulmaktadır: gelişmiş geçirgenlik ve tutma (EPR) etkisi yoluyla pasif hedefleme, ligandlar ve antikorlar kullanılarak aktif hedefleme ve uyarıcıya duyarlı ilaç dağıtım sistemleri. Nanoteknolojinin meme kanseri tedavisine entegre edilmesi, daha hassas, verimli ve kişiselleştirilmiş tedavi seçeneklerinin önünü açarak hasta sonuçlarının iyileştirilmesi için yeni umutlar sunmaktadır.

Anahtar Sözcükler: Meme Kanseri, İlaç Dağıtım Sistemleri, Nanopartikül

1. Introduction

Cancer, a complicated and severe group of diseases defined by uncontrolled cell proliferation and tissue invasion, presents a serious threat to global healthcare systems [1]. Breast cancer is one of the most common and investigated cancers, with numerous subtypes depending on molecular features [2]. The mortality rate for women diagnosed with breast cancer was around 30% in 2022. Breast cancer continues to pose a significant challenge to worldwide health, even with advancements in early diagnosis and therapeutic approaches [3]. Genetic predisposition, late-stage diagnosis, and inadequate access to healthcare remain significant challenges [4].

Breast cancer is complex, and knowing its heterogeneity is critical to develop targeted therapy methods [5]. Recent research has shed light on the molecular complexities and identifying multiple subtypes with varied clinical features and treatment outcomes [6]. The

identification of molecular markers such as human epidermal growth factor receptor 2 (HER2) and hormone receptor statuses has transformed treatment methods, allowing for targeted therapy approaches such as Herceptin in HER2-positive breast cancer [7]. Despite advancements, late-stage diagnosis still poses a significant problem. Early detection has been improved through screening programs and the development of enhanced imaging techniques. Genetic propensity, as indicated by the BRCA1 and BRCA2 mutations, is very important in assessing and preventing breast cancer [8].

Depending on the type and stage of the tumor, current treatment techniques include surgery, radiation therapy, hormone therapy and chemotherapy [9]. While these treatments have made significant progress in improving the lives of patients, they have some negative aspects. Chemotherapy and radiation therapy typically cause serious adverse effects such as exhaustion and nausea, whilst surgical therapies can include complications following surgery and organ damage [10]. Furthermore, traditional treatments may have limited effect, especially in metastatic cancer types, and may unintentionally promote resistance to drugs. In addition, high financial costs can have a significant influence on patients' financial stability and well-being [11].

Traditional medications play an important role in the treatment of cancer, collaborating with new targeted therapies and immunotherapies to achieve better results. Adjuvant radiation treatment, for example, has significantly boosted survival rates while lowering the risk of recurrence [12]. Immunotherapy has become known as an efficient strategy for breast cancer in recent years. Clinical trials are being conducted for examining immune checkpoint inhibitors, which utilize the immune system to fight cancer cells. Some examples of these inhibitors are programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) [13]. With the help of genetics and biomarker studies, personalized medicine optimizes therapeutic outcomes by creating treatment plans that are tailored to each patient's particular cancer tendency [14].

Targeted drug delivery systems are critical in cancer therapy since they improve the effectiveness of drugs by accurately delivering drugs to tumor areas, raising drug concentration in the intended area while decreasing off-target effects [15]. Additionally, these methods make it easier to get across biological barriers like the blood–brain barrier, which makes it possible to transport drugs to areas that would otherwise be inaccessible. Furthermore, targeted drug delivery systems provide personalized treatment approaches, improving therapeutic outcomes and minimizing side effects [16]. Moreover, targeted drug delivery systems have attracted lots of interest in the treatment of breast cancer.

2. Nanoparticles as Targeted Drug Delivery Systems

Nanoparticles are particles which are 1-100 nm in size with an exterior layer of diverse organic or inorganic coatings. Many studies have been carried out to take advantage of nanoparticles in drug delivery systems for breast cancer therapy. However, they have not yet been commonly employed in clinical treatments. Nanoparticles have gained popularity as nanocarriers because of their properties such as water dispersibility, biodegradability and biocompatibility. The bioavailability of many chemotherapeutic treatments is increased when nanoparticles are used to treat cancer because they increase the solubility and half-life of the drugs [17]. Additionally, nanoparticles may promote accumulation of drugs in cancer tissues by EPR effect [18].

Finally, using target ligands to target particular cancer locations, nanoparticle-based drug delivery systems can decrease adverse effects and increase therapy efficacy [19]. Several types of nanoparticles have been used in targeted drug delivery systems for breast cancer. Figure 1 presents a schematic overview of five widely utilized nanoparticle types in drug delivery. Several features of liposomal, polymer-, metal-, carbon-, and mesoporous silica nanoparticles will be explained below.

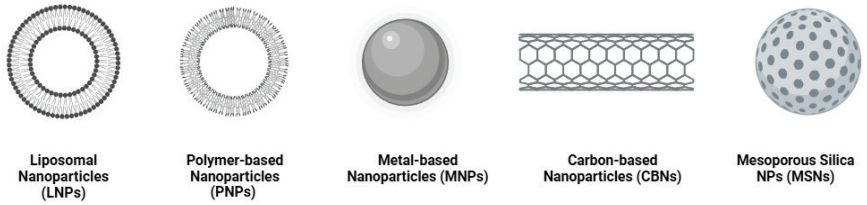

Figure 1. Schematic Illustration of Common Nanoparticle Types in Drug Delivery Systems

This figure presents a schematic overview of widely utilized nanoparticle types in drug delivery: (A) Liposomal Nanoparticles (LNPs), (B) Polymer-based Nanoparticles (PNPs), (C) Metal-based Nanoparticles (MNPs), (D) Carbon-based Nanoparticles (CBNs), (E) Mesoporous Silica Nanoparticles (MSNs).

2.1. Liposomal Nanoparticles (LNPs)

LNPs are spherical vesicles formed by integrating one or more phospholipid bilayers and their size may exceed hundreds of nanometers. These nanoparticles have a hydrophilic inner core that is covered by a hydrophobic lipid bilayer. Due to its distinct form, the phospholipid bilayer is typically used to encapsulate hydrophobic drugs for delivery. LNPs are additionally used for hydrophilic drugs through encapsulation in the inner core. Because of non-target dispersion, encapsulation of drugs significantly lowers the toxicity of drugs. In addition, it is possible to encapsulate amphiphilic drugs, including doxorubicin (Dox), inside of the inner core of LNP. This has been demonstrated to specifically lower Dox's cardiocytotoxicity when compared to its unencapsulated form [20].

LNPs accumulate in cancer tissue via integrating the bilayer across the membrane of cells. Studies have shown that surface modification of liposomal nanoparticles with PEG results in longer half-lives and increased targeting success [21]. PEGylated LNPs demonstrated

successful passive targeting in studies. Also, LNPs have been employed to encapsulate multiple drugs in order to deliver drug combinations that have synergistic effects. Vincristine and quercetin were encapsulated together in a PEGylated liposome by Wong and Chiu to treat breast cancer that is unresponsive to trastuzumab and hormones. According to this study, co-encapsulation promoted more synergism, extended circulation of drugs in plasma with regulated release for JIMT-1 cells in vivo. Furthermore, compared to the two separate drugs, liposomal encapsulation is the most successful method for inhibiting the proliferation of JIMT-1 cells [22].

Doxil®/Caelyx®, Myocet®, Lipodox®, and Lipusu® are the four liposomal drugs that have been licensed for use as breast cancer therapy and have undergone clinical testing. The first chemotherapeutic nanosystem to be used in clinical settings, Doxil® is a PEGylated nano-liposomal drug delivery system loaded with DOX for metastatic breast cancer. The liposomal formulation and its PEGylation are regarded as innovative since they increase the chemotherapeutic agent's circulation time while lowering the blood's level of free DOX without compromising its anticancer action [23].

2.2. Polymer-based Nanoparticles (PNPs)

PNPs are colloidal particles with a size around 100-400 nm. They are typically created via attaching a copolymer onto a different polymer matrix. Natural polymers such as cellulose and chitosan can be employed in this application [60]. However, synthetic polymers can also be utilized to create PNP that fulfill particular chemical and biological purposes, which makes them extremely desirable for use in biomedical fields [24]. PNPs are chemically synthesized using standard techniques such as nanoprecipitation, salting-out, and emulsification [25]. Chemically synthesized PNPs may be engineered to have the necessary charge, lipophilicity, and biocompatibility for transporting the given drug into its target [26].

Delivering the anti-cancer drug to the target region, it can be encapsulated in a PNPs, loaded onto the surface of the PNPs through surface adsorption, as well as chemically conjugated [27]. Most PNPs are efficient carriers for drugs that are less hydrophilic due to their permeability and high solubility, which enables them to maintain stability with a prolonged, gradual release of the drug. Furthermore, PNPs have shown low toxicity and great drug loadability, particularly when capped with a PEG-phospholipid copolymer [28]. Several chemotherapeutic drugs, including Doxorubicin, trastuzumab, and cisplatin, have been explored for PNP and drug conjugation. Several PNPs, such as polyhydroxyalkanoates, PLGA, and cyclodextrin-derived PNPs, were investigated as nanocarriers in cancer therapy [26].

2.3. Metal-based Nanoparticles (MNPs)

MNPs, commonly referred to as inorganic nanoparticles, have been intensively investigated for medicinal and imaging features. Their typical composition consists of an organic-coated shell and a core that determines electrical, magnetic, and optical properties. Gold nanoparticles (AuNPs), superparamagnetic iron oxide nanoparticles (SPIONs), and quantum dots (QDs) are three common varieties utilized in breast cancer treatment [29].

AuNPs have been produced by modifying their size, shape, and surface functionalities for a range of uses [30]. Most popular method for synthesizing AuNPs is to reduce Au3+ in aqueous medium with citrate. These nanoparticles were frequently employed as drug delivery systems due to its special properties and notably low toxicity [31]. For the nanoparticles to target particular receptors or biomarkers, organic surface coating is essential. Because of these surface coatings, thiolates and disulfides are frequently utilized primarily because of their propensity to adhere to the surface of Au. Covalent or non-covalent bonds can then be used to attach drugs or other therapeutic substances to the surface of AuNPs [32]. By targeting EGFR/

VEGFR-2, enhances angiogenesis and cell proliferation, plays an essential role in metastasis of breast cancer, a study demonstrated a significant suppression of breast cancer. Based on this research, AuNPs containing quercetin may suppress the epithelial-mesenchymal transition, and that is a factor of MCF-7 and MDA-MB-231 breast cancer cell lines [33]. Because of their distinctive properties, particularly their controlled functionalization and ease of imaging using microscopic methods like transmission electron microscopy (TEM), AuNPs were commonly used in drug delivery. Despite the low cytotoxicity, AuNPs may have a significant disadvantage in terms of biodegradability in a biological system [29].

SPIONs are ranging in size from 1-100 nm. They contain a magnetic inner core made from magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3). One of the best inner core materials for SPIONs is thought to be maghemite. since it has the lowest risk of toxicity of Fe(III) in the body, as opposed to Fe(II) released by magnetite [34]. One major drawback of using them directly in therapeutic and biological applications is that they may produce biofouling and aggregation in blood plasma [35]. Thus, a hydrophilic coating, like polymers, is applied to the magnetic core to stabilize it and allow for targeted delivery of molecules to particular areas. Polysaccharides, PEG, dextran, and alginate are among the most extensively utilized biopolymers for stabilization [36]. Du et al. utilized ultrasmall iron oxide nanoparticles (IONPs) modified with a breast cancer brain metastasis-targeting peptide (BRBP1), enhancing imaging contrast and tumor specificity [37]. Similarly, Zheng et al. developed self-illuminating nanoprobes targeting neutrophil infiltration, achieving 98% sensitivity and 96% specificity in detecting lung metastases. These approaches highlight the potential of nanoparticle-based imaging for early metastasis detection, supporting more precise, personalized breast cancer treatment [38].

QDs are semiconductor nanocrystals with diameters ranging from 2-10 nm. They are generally made up of a metal inner core that emits a narrow range of visible to infrared (IR) light based on size. Depending

on its intended use, the shell could be made of semiconductor layers or doped metals. When QDs are conjugated with surface modifying ligands and peptides, they can be utilized for cancer investigations with targets [39]. QDs made it possible to image cells in vivo much more than most other NPs because of their good adjustable optical characteristics, high brightness, resistance to photobleaching and large surface-to-volume ratio. Nonetheless, one disadvantage of QDs is their extreme hydrophobicity. They need to have polymers or multilayer ligand shells applied to their surface in order to reach an ideal level of water solubility [40]. The main disadvantage of these nanoparticles is that their inner core is often composed of heavy metals, which may be hazardous to the body in the long term due to accumulation in organs like the liver. Furthermore, QDs' exceptional stability reduces their biodegradability and, consequently, their biocompatibility. As a result, recent research has concentrated on non-metal nanoparticles as an alternative to traditional metal-based QDs [29].

Nanoparticle-based platforms also show promise in detecting circulating tumor cells (CTCs), offering insights into metastasis and cancer progression [41]. Since CTCs are key indicators of metastatic disease, their early detection is crucial for timely, personalized treatments. Wang M et al. developed a fluorescent technique using peptide-functionalized magnetic nanoparticles to quantify HER2 on CTCs, providing both prognostic data and potential guidance for therapy decisions [42].

2.4. Carbon-based Nanoparticles (CBNs)

CBNs, such as fullerene, graphene, carbon nanotubes (CNTs), and carbon dots (CDs), are attractive tools for treating breast cancer because of their distinct biological, physicochemical, optical features [43]. CBNs were designed to replace hazardous, heavy-metal-containing QDs and other metal nanoparticles with a nonmetallic system. CBNs have various advantages, including high specific surface area,

biocompatibility, small size, variable surface functional groups, low toxicity, and distinct optical and thermal properties. Thus, CBNs might be considered a better and prospective drug delivery system to be used in cancer therapy than metal-based nanoparticles [44].

CNTs are fullerene allotropes with a cylindrical shape and long, hollow structures having a wall made of graphene sheet coiled at an angle. CNTs are divided into single-walled and multi-walled types according to whether they have one or more graphene sheets. CNTs are still being developed, and they show many remarkable qualities, including electrical, optical, and thermal conductivity. Furthermore, CNTs have emerged as a multipurpose tool for the use of nanomedicine, especially in cancer targeting [45]. Since biological systems are extremely transparent in near-infrared (NIR) light, CNTs can be used as an efficient optical absorber because of their tunable surface and special thermal properties [46]. Drug loading into CNTs may be difficult because they are pre-formed supramolecular nanotubes. Direct loading to the surface and filament loading are the two drug loading patterns of CNTs. They can be filled with drugs using a simple capillarity-induced filling method. However, the loadable amount of drugs might be 5% (w/w) [47].

CDs a novel family member of carbon-based nanoparticles. When they first discovered, the majority of the research focused on photoluminescence (PL) employing different synthetic methods, starting materials, and surface changes [48]. Surface doping boosted fluorescence quantum yield (QY) as a PL measurement by up to 93.3% [49]. Hsu et al. demonstrated that green tea-derived CDs inhibited cancer cell growth. Three cancer cell lines were used: MCF-7, MDA-MB-231, and HeLa. While the concentration of CDs increased, the viability of cells decreased. According to their respective cell viability percentages of 20, 18, and 68%, MCF-7, MDA-MB-231, and HeLa cells showed a significant inhibitory effect on breast cancer cell lines when using CDs [50].

2.5. Mesoporous Silica Nanoparticles (MSNs)

MSNs received a lot of interest as a different inorganic nanoparticle in targeted drug delivery and imaging because of their distinctive characteristics, such as pore volume, large surface area, and the ability to vary pore size beside providing a surface that can be easily modifiable [51]. The unique porous surface of MSNs allows for a high and controlled drug loading capacity. They can also carry medications without releasing them prematurely before they reach their target site, making them an excellent carrier for molecules that degrade easily, such as proteins and DNA. In order to selectively target breast cancer cells, a study reported an anti-HER2/neu monoclonal antibody based on nanoparticles and employing green fluorescent MSNs as drug carriers [52]. In another study, researchers created an MSNs drug delivery system to deliver siRNA for reducing Dox resistance in multi drug resistance breast cancer cells in mice [53].

3. Targeting Strategies For Breast Cancer Therapy

The treatment of breast cancer has been mostly transformed by targeted drug delivery systems, which have the potential to improve therapeutic effect while lowering systemic toxicity. This may be developed to circumvent drug resistance processes, which commonly hinder therapeutic outcomes [54]. Targeted drug delivery has a high promise for overcoming resistance to drugs by improving delivery of drugs to cancer cells that are resistant or using combination treatments that focusing several pathways [55]. Figure 2. shows an illustration of drug delivery strategies. This part goes into several targeting strategies for improving the delivery of drugs, particularly for breast cancer, focusing on developments and their clinical consequences.

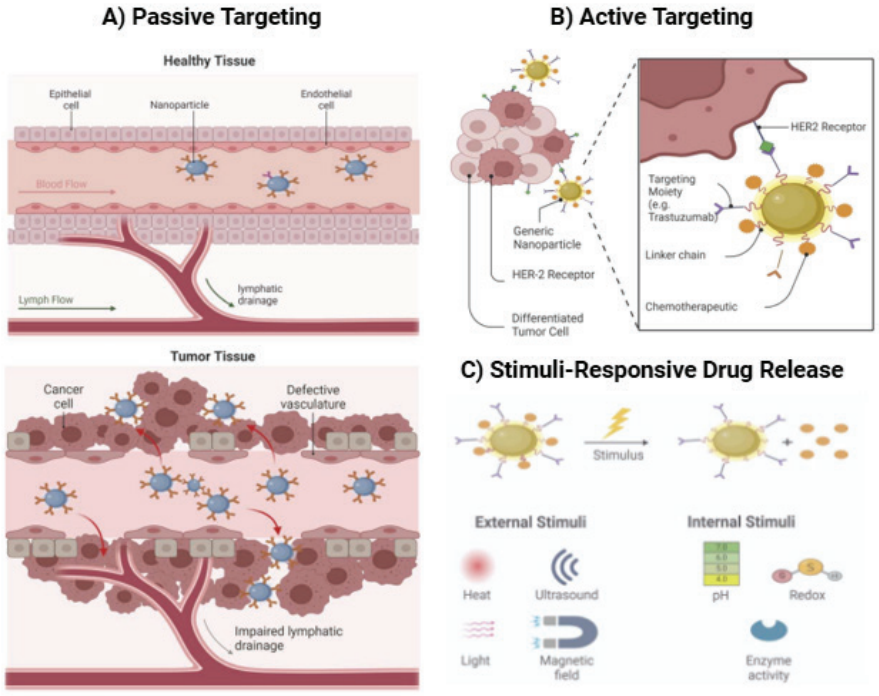

Figure 2. Schematic Illustration of Drug Delivery Strategies

This figure illustrates three major strategies employed in targeted drug delivery systems: (A) Passive Targeting, (B) Active Targeting, (C) Stimuli-Responsive Drug Release.

3.1. Passive Targeting

In breast cancer treatment, passive targeting is based on a basic phenomenon called the increased permeability and retention (EPR) effect. This impact is achieved using unique properties of the tumor microenvironment [56]. Some solid tumors have abnormal blood vessels which provide nutrition to the tumor. Due to their irregular form and leakiness, nanoparticles can passively infiltrate the tumor tissue [57]. These nanoparticles tend to gather within the tumor because of

poor lymphatic drainage. In cancer, the lymphatic system, which is in charge of removing waste and fluid from tissues, is frequently weakened, which makes nanoparticles more likely to remain in the tumor microenvironment [58].

Optimizing the design of drug carriers and nanoparticles to maximize the EPR effect has been the focus of recent studies. Particle size, drug release profiles, and surface charge are precisely set for optimizing drug delivery while minimizing off-target effects. Researchers intend to enhance breast cancer therapy selectivity and efficacy by leveraging the EPR effect [59].

3.2. Active Targeting

Active targeting techniques employ a more accurate method by actively guiding drug delivery systems to their target cancer cells using particular molecules, like ligands, antibodies or peptides. Targeting moieties are chosen for their high affinity in binding to overexpressed receptors on cancer cell surfaces [60]. When these targeting ligands are coupled with drug carriers like nanoparticles, liposomes, or exosomes, It is possible to precisely target drug delivery to the tumor area. By using this technique, the negative effects of therapeutic drugs are greatly reduced in off-target effects and healthy tissues can be protected [61].

Creating antibody-drug conjugates (ADCs) to specifically treat breast cancer represents a significant advancement in this field. ADCs are monoclonal antibodies that target receptors on the surface of cancer cells and deliver powerful cytotoxic cargoes. This enables a very specific and powerful treatment strategy. The drug is directly delivered to the cancer cell by the antibody, thus promoting apoptosis in cancer cell while preserving healthy cells [62].

3.3. Stimuli-Responsive Drug Delivery Systems

One of the most innovative approaches to breast cancer therapy is the use of stimuli-responsive drug delivery systems. These systems release therapeutic drugs based on certain parameters in the tumor microenvironment. These variables may include pH, temperature or enzyme activity variations that are particular to cancer cells. Drug delivery systems that are stimulus-responsive are designed to react to these signals, guaranteeing release of the drugs inside the tumor while preserving healthy tissue. As an example, the acidic environment of breast cancer may be used as an initiator for the release of drugs [63]. The acidic environment in the tumor tissue causes nanoparticles or carriers to release the therapeutic payload as they enter, lowering negative effects in surrounding tissues and enhancing drug exposure to cancer cells [64].

This strategy has various benefits, such as decreased systemic toxicity and enhanced drug absorption at the target location. It has enormous potential to improve the therapeutic effect in breast cancer treatment.

4. Conclusions

Nanoparticle-based drug delivery systems have become a game-changer in the treatment of breast cancer since they provide better drug solubility, more precise tumor targeting, and less systemic toxicity. By utilizing their distinct physicochemical characteristics, these nanocarriers which include liposomal, polymer-based, carbon-based, mesoporous silica nanoparticles offer flexible platforms for effective drug delivery. When compared to traditional medicines, they have the potential to greatly improve treatment outcomes by improving drug accumulation at tumor locations and overcoming biological obstacles.

In order to maximize the therapeutic effects of nanoparticles, targeting strategies are essential. Because of abnormal vasculature and

impaired lymphatic drainage, passive targeting, which is primarily enabled by the increased EPR effect, enables nanoparticles to accumulate in tumor tissues. Active targeting improves selectivity and reduces off-target effects by enabling precise binding to overexpressed receptors on cancer cells using ligands, antibodies, and peptides. Additionally, stimuli-responsive systems, triggered by tumor-specific microenvironmental factors such as pH, temperature, or enzyme activity, provide controlled and localized drug release, further minimizing adverse effects on healthy tissues. Despite these encouraging developments, a number of obstacles need to be overcome in order to facilitate the clinical translation of nanoparticle-based treatments. Long-term toxicity, immunogenicity, large-scale manufacturing, stability, and regulatory approval are still major obstacles. Furthermore, because breast cancer subtypes are diverse, personalized nanomedicine strategies that are suited to each patient's unique profile must be developed. The combination of therapeutic and diagnostic properties in multifunctional nanoparticles offers enormous promise for real-time tracking of disease development and treatment efficacy.

Future studies should concentrate on enhancing targeted delivery efficiency, optimizing nanoparticle formulations for improved biocompatibility, and ensuring safety through thorough preclinical and clinical testing. The development of next-generation nanocarriers will be further accelerated by the convergence of nanotechnology with areas including biomarker-driven precision medicine and genomics. With continued advancements and interdisciplinary collaboration, nanoparticle-based targeted drug delivery systems possess the power to change the treatment of breast cancer, paving the way for more effective and personalized therapeutic approaches.

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