Recent Advances In Targeted Nanoparticle-Based Drug Delivery System For Breast Cancer Therapy: A Comprehensive Review

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Abstract

Breast cancer remains a leading cause of cancer-related deaths among women worldwide. Conventional treatments face challenges such as toxicity, low specificity, and drug resistance. Nanotechnology offers innovative solutions through targeted and controlled drug delivery. Recent advances focus on passive and active targeting strategies for enhanced efficacy. Different nanocarriers—lipid-based, polymeric, inorganic, and hybrid—are being developed. Stimuli-responsive and multifunctional nanoparticle enable combined therapy and diagnosis. Key challenges include scalability, toxicity and regulatory hurdles in clinical translation. Future trends emphasize precision nanomedicine to improve breast cancer treatment outcomes.

Keywords: Nanotechnology, Targeted Drug Delivery, Precision Oncology, Cancer Therapy, Tumor Targeting, Targeted Nanoparticles, Passive and Active Targeting, Stimuli-Responsive Nanocarriers,Tumor Microenvironment, Drug Resistance, Gene and Immuno-Nanotherapy, Clinical Translation.

1.Introduction

Breast cancer is one of the most common and deadly cancers among women worldwide. Although treatments such as surgery, chemotherapy, radiotherapy, and hormonal therapy have improved survival rates, they still face challenges like toxicity, drug resistance, and poor selectivity toward tumor cells. Conventional chemotherapy damages healthy tissues and often causes severe side effects, highlighting the need for safer and more effective targeted therapies. Nanotechnology offers promising solutions for cancer treatment through the use of engineered nanoparticles (NPs). These tiny carriers (10–200 nm) can improve drug delivery by enhancing solubility, stability, and controlled release. Nanoparticles can passively target tumors through the enhanced permeability and retention (EPR) effect and actively target specific cancer cells using ligands such as antibodies, peptides, or folate molecules that bind to receptors overexpressed on breast cancer cells like HER2 and EGFR .Different types of nanoparticles, including liposomes, polymeric nanoparticles, dendrimers, solid lipid nanoparticles, and metallic nanoparticles, have been developed to increase treatment efficiency and reduce side effects. Some of these systems also combine diagnostic and therapeutic functions, known as theranostic nanoparticles, offering great potential for personalized breast cancer therapy. This review summarizes the latest progress in targeted nanoparticles for breast cancer treatment, focusing on their delivery mechanisms, design strategies, and future clinical potential.

2. Breast Cancer Overview

2.1 Epidemiology and Burden

Breast cancer is the most commonly diagnosed malignancy among women, accounting for about 12% of all new cancer cases globally. The World Health Organization (2024) reports that one in eight women will develop the disease during their lifetime. Mortality rates are higher in developing nations due to delayed diagnosis and limited access to treatment. The growing incidence in younger populations and the aggressive nature of subtypes like triple-negative breast cancer (TNBC) further intensify the global health burden.

2.2 Pathophysiology

This cancer originates in the epithelial cells of the breast ducts or lobules and exhibits high biological heterogeneity. Its development is driven by genetic mutations (e.g., BRCA1, BRCA2, HER2, TP53), along with hormonal and environmental influences. Key hallmarks include uncontrolled proliferation, evasion of apoptosis, angiogenesis, and immune system suppression—factors that collectively promote tumor growth and metastasis.

2.3 Classification and Subtypes

Breast cancer is categorized into molecular subtypes with distinct clinical behaviors:

- Luminal A (ER+/PR+, HER2−): Slow-growing and responsive to hormone therapy.
- Luminal B (ER+/PR+, HER2+): More aggressive; requires combined hormonal and targeted therapy.
- HER2-Enriched (ER−/PR−, HER2+): Rapidly dividing; responds to anti-HER2 agents.
- Triple-Negative (TNBC; ER−/PR−/HER2−): Lacks receptor targets, associated with poor prognosis and limited treatment options.

2.4 Current Therapeutic Approaches and Limitations

Conventional treatments—surgery, radiation, and chemotherapy—are primarily effective in early-stage disease. However, systemic toxicity, low selectivity, and resistance often limit success in advanced stages. Drugs like doxorubicin and paclitaxel can damage healthy tissues, while targeted therapies such as trastuzumab benefit only specific subtypes. Moreover, the tumor microenvironment (TME), characterized by hypoxia, poor vascularization, and immune evasion, hinders drug delivery and efficacy. These limitations highlight the need for innovative, precise therapeutic strategies.

2.5 Rationale for Nanoparticle-Based Therapy

Nanoparticle-based drug delivery offers a promising alternative by enhancing therapeutic precision and minimizing side effects. Their nanoscale size and customizable surfaces enable extended circulation and targeted tumor accumulation through passive (EPR effect) and active (ligand-mediated) targeting. These systems improve drug stability, control release rates, and bypass biological barriers, positioning nanomedicine as a powerful tool for advancing breast cancer therapy.

3. Nanoparticle Systems in Oncology

3.1 Overview of Nanomedicine

Nanomedicine integrates principles from material science, chemistry, and biology to engineer nanoparticles (NPs) capable of diagnosing and treating cancer at the molecular level. In oncology, these nanosystems improve drug delivery, imaging, and combination therapies while enhancing stability, biodistribution, and safety compared to conventional treatments. Their nanoscale size (10–200 nm) allows efficient tissue penetration, tumor targeting, and minimized systemic toxicity.

Key benefits include:

- **Enhanced solubility:** Enables delivery of poorly soluble drugs such as paclitaxel.
- **Extended circulation:** Surface modifications like PEGylation reduce immune clearance.
- **Controlled drug release:** Responsive to internal stimuli such as pH or temperature.
- **Co-delivery and theranostics:** Facilitate simultaneous treatment and imaging.

3.2 Major Classes of Nanoparticles in Oncology

- **Lipid-Based Nanoparticles:** Systems such as liposomes and solid lipid nanoparticles can encapsulate both hydrophilic and hydrophobic agents. They are biocompatible and clinically validated, as seen in *Doxil* (liposomal doxorubicin) and *Abraxane* (albumin-bound paclitaxel) for breast cancer.
- **Polymeric Nanoparticles:** Constructed from biodegradable polymers like PLGA, PEG, chitosan, and PLA, they enable controlled drug release and targeted delivery. Polymeric micelles are particularly effective for hydrophobic drugs.
- **Inorganic Nanoparticles:** Materials like gold, iron oxide, and silica possess optical or magnetic features valuable for drug delivery and diagnostic imaging. Gold nanoparticles are often applied in photothermal therapy, where localized heat destroys tumor cells.
- **Hybrid and Multifunctional Nanoparticles:** These combine organic and inorganic components, integrating biocompatibility with imaging and therapeutic functions. They can simultaneously support drug and gene delivery, advancing personalized cancer treatment.

3.3 Mechanisms of Nanoparticle Drug Delivery

Following administration, nanoparticles circulate in the bloodstream, preferentially accumulate in tumor tissues, and release therapeutic agents inside cancer cells. Cellular uptake mainly occurs via endocytosis, after which drugs are liberated in the cytoplasm. Delivery efficiency depends on particle characteristics such as size, surface charge, hydrophobicity, and ligand attachment.

3.4 Clinical Relevance and Approved Nanomedicines

Several nanoparticle-based formulations have achieved clinical success, improving efficacy and reducing toxicity:

- **Doxil:** PEGylated liposomal doxorubicin for breast and ovarian cancers.
- **Abraxane:** Albumin-bound paclitaxel enhancing solubility and safety.
- **Onivyde:** Liposomal irinotecan approved for advanced malignancies.
- **MM-302:** HER2-targeted liposomal doxorubicin currently under clinical evaluation for HER2-positive breast cancer.

4. Passive Targeting Mechanisms (EPR)

4.1 Concept of Passive Targeting

Passive targeting relies on the Enhanced Permeability and Retention (EPR) effect, a characteristic of tumor blood vessels. Tumors exhibit rapid, abnormal angiogenesis, resulting in leaky vasculature with large pores (100–800 nm) and poor lymphatic drainage. These features allow nanoparticles to passively accumulate and remain within tumor tissues without the use of targeting ligands, making EPR a fundamental mechanism in nanomedicine-based cancer therapy.

4.2 Factors Affecting the EPR Effect

The effectiveness of passive targeting depends on both tumor properties and nanoparticle design:

- Tumor vasculature: Varies with tumor type, size, and site, influencing nanoparticle accumulation.
- Interstitial fluid pressure (IFP): High IFP can limit nanoparticle penetration into deeper tumor regions.
- Nanoparticle size: Sizes between 50–200 nm are generally optimal for tumor retention.
- Surface charge and hydrophobicity: Neutral or slightly negative particles circulate longer and reduce nonspecific uptake.
- Circulation time: Surface coatings like PEGylation prevent immune recognition, increasing nanoparticle persistence and tumor accumulation.

4.3 Advantages of Passive Targeting

Passive targeting offers several benefits, including simple formulation without specific ligands, reduced systemic toxicity, and broad applicability to various solid tumors. It also serves as a foundational mechanism that can be enhanced further by active targeting strategies to improve therapeutic outcome.

5. Active Targeting Mechanisms

5.1 Concept and Rationale

Active targeting involves functionalizing nanoparticles with specific ligands that bind to receptors overexpressed on cancer cells. Unlike passive targeting, which depends solely on the Enhanced Permeability and Retention (EPR) effect, this strategy enables direct interaction with tumor cells, enhancing drug uptake, intracellular delivery, and overall therapeutic efficiency—especially in cases where the EPR effect is limited.

5.2 Types of Targeting Ligands

A range of ligands can be used to guide nanoparticles to tumor-specific receptors:

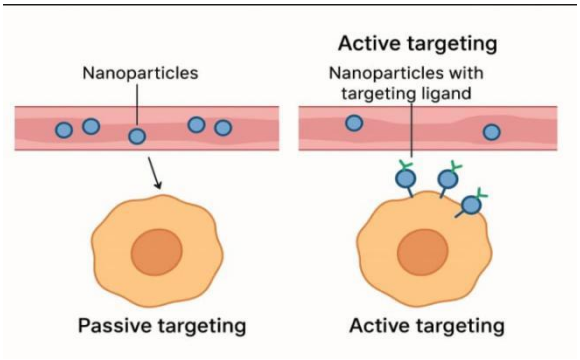
- Antibodies and fragments: Monoclonal antibodies such as trastuzumab (anti-HER2) and cetuximab (anti-EGFR) enable precise targeting of receptor-positive breast cancers. Smaller fragments like Fab or scFv improve tissue penetration and maintain specificity.
- Peptides: Short sequences such as RGD and TAT promote receptor-mediated internalization and exhibit low immunogenicity and high stability.
- Aptamers: These single-stranded DNA or RNA molecules fold into specific 3D structures to recognize target proteins. For example, the AS1411 aptamer binds nucleolin, frequently overexpressed in breast cancer cells.
- Small molecules and vitamins: Ligands such as folic acid, transferrin, and hyaluronic acid are widely used to target receptors commonly found on tumor cell surfaces, improving selective delivery.

5.3 Cellular Uptake Mechanism

Upon ligand–receptor binding, nanoparticles are internalized through endocytic pathways, including clathrin- and caveolae-mediated processes. After entering the cell, efficient drug release requires endosomal escape, often achieved through pH-sensitive coatings. Active targeting not only enhances intracellular drug retention but also helps overcome multidrug resistance by minimizing drug efflux and ensuring sustained therapeutic action.

5.4 Schematic illustration:

Schematic illustration of passive and active nanoparticle targeting mechanism.



6. Concept and Rationale:

Active targeting enhances nanoparticle delivery by using ligands that specifically recognize and bind to receptors overexpressed on cancer cells. Unlike passive targeting, which depends only on the Enhanced Permeability and Retention (EPR) effect, active targeting allows precise interaction at the cellular level. This approach improves drug uptake, intracellular transport, and treatment efficiency, especially in tumors where EPR alone is insufficient.

6.1Types of Targeting Ligands:

Various ligands have been used to modify nanoparticles for receptor-specific targeting:

1. Antibodies and Fragments:

Monoclonal antibodies like trastuzumab (anti-HER2) and cetuximab (anti-EGFR) are attached to nanoparticles for selective delivery to HER2- or EGFR-positive breast cancer cells. Smaller antibody fragments (Fab, scFv) provide better tissue penetration while maintaining high specificity.

2. Peptides:

Short peptides such as RGD and TAT enhance receptor-mediated uptake or membrane penetration. They are easy to synthesize, stable, and show low immunogenicity.

3. Aptamers:

Aptamers are short DNA or RNA strands that form unique 3D shapes to bind target molecules. For example, the AS1411 aptamer binds to nucleolin, commonly overexpressed in breast cancer cells.

4. Small Molecules and Vitamins:

Ligands like folic acid, transferrin, and hyaluronic acid are frequently used since their receptors are abundant on tumor cells. Folic acid–modified nanoparticles effectively target folate receptor–positive breast cancers.

5. Cellular Uptake Mechanism:

After ligand–receptor binding, nanoparticles enter cells through endocytosis pathways such as clathrin- or caveolae-mediated processes. Once internalized, successful therapy depends on the nanoparticle's ability to escape endosomes and release the drug into the cytoplasm. Designing pH-sensitive coatings can promote this release. Active targeting also improves drug retention in tumors and reduces multidrug resistance by limiting drug efflux.

Target Receptor	Ligand/Nanoparticle used	Therapeutic Advantage
HER2/Neu	Trastuzumab-Conjugated Liposomes gold NPs	Selective action in HER2-positive cells
Estrogen Receptor	Estrogen-Functionalized PLGA NPs	Enhanced uptake in ER-positive tumors
Folate Receptor	Folic acid-linked polymeric micelles	Specific delivery to folate-rich cancer cells
CD44 Receptor	Hyaluronic acid-based NPs	Targeting of invasive triple-negative breast cancer
Transferring Receptor	Transferrin-coated solid lipid NPs	Improved intracellular drug transport

Dual and Multimodal Targeting

To further increase specificity, nanoparticles can carry two or more ligands that target multiple receptors. For example, combining folate and transferrin ligands improves binding efficiency and tumor accumulation. Some advanced systems also integrate stimuli-responsive elements (like pH or redoxsensitivity), allowing controlled drug release and combining therapeutic and diagnostic (theranostic) functions in one platform.

Limitations and Future Prospects

Although active targeting shows great promise, challenges remain. Tumor receptor heterogeneity can limit uniform nanoparticle distribution. The high cost and stability issues of biological ligands also affect scalability. Future research focuses on biomimetic nanoparticles, such as those coated with cell membranes, and AI-guided receptor profiling to achieve more personalized and efficient cancer targeting.

6. Types of Nanoparticles for Breast Cancer Therapy

6.1 Overview

Nanoparticles are engineered in diverse forms to enhance the precision, safety, and therapeutic success of breast cancer treatments. Based on their composition, they are broadly classified into lipid-based, polymeric, inorganic, protein-based, and biomimetic systems—each offering unique structural and functional benefits for targeted drug delivery.

6.2 Lipid-Based Nanoparticles

6.2.1 Liposomes:

Liposomes are spherical vesicles composed of lipid bilayers surrounding an aqueous core, capable of encapsulating both hydrophilic and hydrophobic drugs. They are biocompatible and minimize systemic toxicity.

Examples:

- Doxil – liposomal doxorubicin, the first FDA-approved nanodrug for breast and ovarian cancer.
- MM-302 – HER2-targeted liposomal doxorubicin under clinical evaluation.
- ThermoDox – heat-sensitive liposome that releases drugs at elevated temperatures.

Advantages: Long circulation time and controlled release.

Limitations: Stability challenges and restricted tissue penetration.

6.2.2 Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs):

SLNs and NLCs consist of solid or mixed lipid matrices that improve drug stability and loading efficiency. Paclitaxel-loaded SLNs have shown enhanced antitumor activity and reduced hypersensitivity. NLCs overcome crystallization issues common in SLNs and provide higher drug-loading capacity.

6.3 Polymeric Nanoparticles

Constructed from biodegradable polymers such as PLGA, PEG, PCL, and chitosan, polymeric nanoparticles can be customized for passive or active targeting.

6.3.1 Polymeric Micelles:

Composed of a hydrophobic core and hydrophilic shell, micelles are ideal for encapsulating poorly soluble drugs. Genexol-PM (PEG-PLA micelles with paclitaxel) is approved for breast cancer therapy.

Advantage: Enhanced solubility and tumor accumulation.

6.3.2 Dendrimers:

Highly branched polymers with tunable size and multiple surface groups for precise drug conjugation. PAMAM dendrimers coupled with folic acid and doxorubicin target folate receptor–positive breast cancer.

Advantage: High drug-loading capacity and surface modification flexibility.

6.3.3 Chitosan Nanoparticles:

Positively charged, biodegradable carriers that promote cellular uptake, suitable for oral and transdermal drug delivery applications.

6.4 Inorganic Nanoparticles

6.4.1 Gold Nanoparticles (AuNPs):

Known for their optical and thermal properties, AuNPs are used in photothermal therapy (PTT) and imaging. Trastuzumab-conjugated AuNPs specifically target HER2-positive breast cancer.

Advantage: High stability, easy surface modification, and dual diagnostic–therapeutic potential.

6.4.2 Magnetic Nanoparticles (Fe_3O_4):

Applied in magnetic hyperthermia and MRI imaging, they can be directed toward tumors using external magnetic fields. Doxorubicin-loaded Fe_3O_4 nanoparticles exhibit synergistic chemo-hyperthermia effects.

6.4.3 Mesoporous Silica Nanoparticles (MSNs):

Characterized by a large surface area and tunable pores for controlled drug release. Folic acid–modified MSNs delivering curcumin and paclitaxel show enhanced anticancer activity.

Advantage: Stimuli-responsive release and minimal toxicity.

6.5 Protein-Based Nanoparticles

These nanoparticles employ natural proteins such as albumin, gelatin, or ferritin for safe and efficient drug delivery.

Examples:

- Abraxane® (albumin-bound paclitaxel) – improves solubility and reduces allergic reactions.
- Ferritin nanoparticles – target transferrin receptors for selective uptake.

Advantage: Biodegradability and non-immunogenicity.

6.6 Biomimetic Nanoparticles

Biomimetic nanoparticles mimic natural cell membranes (e.g., red blood cells, platelets, or cancer cells) to evade immune detection and improve targeting.

Examples:

RBC membrane–coated nanoparticles for prolonged circulation.

Cancer cell membrane–coated nanoparticles enabling homotypic tumor recognition.

Advantage: Immune evasion, extended circulation, and superior tumor selectivity.

7. Stimuli-Responsive and Smart Nanoparticles

7.1 Concept of Smart Nanoparticles

Traditional nanoparticle systems provide sustained or passive drug release; however, smart nanoparticles (also called stimuli-responsive nanoparticles) can release therapeutic agents in response to specific internal or external triggers. These stimuli correspond to physiological or environmental changes within tumors, ensuring spatiotemporal control of drug delivery. Such responsiveness enhances tumor selectivity, reduces off-target toxicity, and allows on-demand drug activation at the disease site.

Stimuli can be classified as:

- Internal stimuli: pH, redox potential, enzymes, ATP concentration, and hypoxia.
- External stimuli: temperature, magnetic field, ultrasound, and light (especially near-infrared, NIR)

7.2 Internal Stimuli-Responsive Systems

(a) pH-Responsive Nanoparticles

Tumor microenvironments are typically more acidic (pH 6.5–6.8) than normal tissues (pH 7.4), while intracellular endosomes/lysosomes can be even lower (pH 4.5–5.5). pH-responsive nanoparticles are engineered using acid-labile linkages (e.g., hydrazone, imine, or acetal bonds) that degrade in acidic conditions, enabling targeted drug release.

Example:

Doxorubicin-loaded PLGA nanoparticles with pH-sensitive hydrazone linkers released >80% of drug content under acidic tumor conditions but remained stable in normal physiological pH.

(b) Redox-Responsive Nanoparticles

Tumor cells have elevated intracellular glutathione (GSH) levels—up to 1000× higher than extracellular environments. Redox-sensitive nanoparticles utilize disulfide (-S–S-) bonds that cleave in reducing conditions, releasing the drug only within cancer cells.

Example:

Paclitaxel-loaded disulfide-crosslinked polymeric micelles exhibit enhanced drug release within breast cancer cells with high GSH content.

(c) Enzyme-Responsive Nanoparticles

Matrix metalloproteinases (MMPs), cathepsins, and hyaluronidases are overexpressed in tumor tissues. Nanoparticles incorporating enzyme-cleavable linkers degrade selectively within enzyme-rich tumor sites.

Example:

MMP-sensitive liposomes modified with peptide substrates release doxorubicin specifically in invasive breast tumors, reducing systemic toxicity.

(d) Hypoxia-Responsive Nanoparticles

Due to abnormal vasculature, tumor tissues often suffer from hypoxia (low oxygen tension). Hypoxia-sensitive nanoparticles release drugs upon reduction of nitroaromatic or azo groups under hypoxic conditions.

Example:

Nitroimidazole-modified polymeric nanoparticles demonstrated controlled release of camptothecin under hypoxia, improving cytotoxicity against hypoxic TNBC cells.

7.3 External Stimuli-Responsive Systems

(a) Thermo-Responsive Nanoparticles

Mild hyperthermia (40–43 °C) can increase membrane permeability and enhance drug diffusion. Thermo-sensitive liposomes such as ThermoDox release doxorubicin upon localized heating, triggered by focused ultrasound or laser irradiation.

(b) Magnetic Field–Responsive Nanoparticles

Magnetic nanoparticles (Fe_3O_4) generate heat when exposed to an alternating magnetic field—known as magnetic hyperthermia. This effect induces apoptosis in tumor cells while simultaneously triggering drug release.

Example: Fe_3O_4 nanoparticles encapsulated with doxorubicin have shown synergistic chemo-hyperthermic cytotoxicity against breast cancer cell lines.

(c) Photo-Responsive Nanoparticles

Light-responsive systems use photosensitizers or photo-labile linkers that release drugs upon exposure to specific wavelengths (e.g., near-infrared).

Example: Gold nanorods conjugated with doxorubicin release the drug upon NIR irradiation, combining photothermal ablation and chemotherapy.

(d) Ultrasound-Responsive Nanoparticles

Ultrasound waves induce mechanical oscillations and cavitation, leading to the rupture of nanoparticle shells and localized drug release.

Example: Ultrasound-sensitive perfluorocarbon nanoparticles have been used to deliver doxorubicin and siRNA in combination therapies for breast cancer.

7.4 Multi-Stimuli-Responsive Nanocarriers

To overcome tumor heterogeneity, researchers have developed multi-stimuli-responsive systems that respond to multiple triggers (e.g., pH + redox, or enzyme + temperature). These dual-or tri-responsive nanoplatforms provide superior precision and dynamic adaptability to the tumor microenvironment.

Example:

pH/redox dual-sensitive nanoparticles encapsulating doxorubicin and curcumin demonstrated synergistic anticancer activity with controlled sequential release in breast cancer xenografts.

7.5 Advantages of Smart Nanoparticles

- High spatiotemporal drug control
- Reduction in systemic toxicity
- Synergistic therapy via co-delivery of multiple agents

8. Theranostic Nanoparticles and Imaging Integration

8.1 Concept of Theranostics

The term "theranostics" refers to the integration of therapeutic and diagnostic capabilities into a single nanoplatform. Theranostic nanoparticles enable simultaneous imaging, targeted drug delivery, and real-time monitoring of treatment response. This dual functionality allows clinicians to visualize nanoparticle biodistribution, quantify drug accumulation, and adapt therapy dynamically—paving the way for personalized and precision oncology.

8.2 Design Principles of Theranostic Nanoparticles

To achieve effective theranostic performance, nanoparticles must incorporate both:

1. Therapeutic components — anticancer drugs, photosensitizers, or gene materials.

2. Imaging agents — fluorescent dyes, magnetic materials, radionuclides, or contrast agents.

The challenge lies in designing biocompatible, stable systems that maintain both imaging

visibility and therapeutic potency in vivo.

8.3 Imaging Modalities Integrated with Nanoparticles

(a) Magnetic Resonance Imaging (MRI)

Magnetic nanoparticles, especially superparamagnetic iron oxide nanoparticles (SPIONs), act as efficient MRI contrast agents. By coupling drugs or targeting ligands, these nanocarriers provide both therapy and imaging functions.

Example: Doxorubicin-loaded SPIONs conjugated with folic acid allow MRI visualization of tumor accumulation while simultaneously delivering chemotherapy.

b) Florescence Imaging

Quantum dots (QDs) and near-infrared (NIR) fluorescent dyes can be integrated with nanoparticles for real-time optical imaging of tumor sites.

Example: NIR-emitting silica nanoparticles conjugated with trastuzumab demonstrated

HER2-specific tumor imaging and doxorubicin delivery in vivo.

However, toxicity concerns associated with cadmium-based QDs have led to the development of biodegradable carbon dots as safer alternatives.

(c) Computed Tomography (CT)

High-atomic-number elements such as gold (Au) and bismuth (Bi) serve as CT contrast enhancers. Gold nanoparticles are particularly useful for dual CT imaging and photothermal therapy due to their strong X-ray attenuation and optical absorption.

(d) Positron Emission Tomography (PET)

Nanoparticles labelled with radionuclides (e.g., ^64Cu, ^68Ga) allow PET-based tracking of biodistribution and pharmacokinetics.

Example: ^64Cu-labeled liposomes provide quantitative insights into drug accumulation within tumors.

(e) Photoacoustic and Ultrasound Imaging

Hybrid nanoparticles that absorb light or respond to ultrasound waves generate acoustic signals detectable via noninvasive imaging.

Example: Gold nanorods coated with perfluorocarbon demonstrated photoacoustic visualization alongside oxygen delivery in hypoxic tumors.

8.4 Multifunctional Theranostic Nanoplatforms

Researchers have developed multimodal theranostic systems that combine several imaging and treatment modes in one construct.

For example: Au–Fe_3O_4 core–shell nanoparticles: permit MRI, CT, and photothermal therapy.

Liposome–quantum dot hybrids: enable fluorescence imaging and chemotherapy.

Carbon nanodots loaded with siRNA: achieve gene silencing and real-time fluorescence tracking.

8.5 Theranostics in Breast Cancer

Breast cancer presents specific opportunities for theranostic application due to

well-characterized receptor targets and accessible imaging modalities.

Examples include:

HER2-targeted gold nanoshells integrating trastuzumab and doxorubicin for combined chemotherapy and photothermal ablation.

Folate-decorated SPIONs for dual MRI imaging and delivery of paclitaxel to folate receptor–positive cells.

NIR fluorescent carbon dots conjugated with siRNA for visual tracking of gene silencing efficiency in TNBC models.

8.6 Clinical Translation and Challenges

While preclinical studies show remarkable promise, translation into clinical practice remains 2limited due to challenges in:

Complex synthesis and reproducibility of multifunctional nanoplatforms.

Regulatory hurdles in approving hybrid diagnostic–therapeutic systems.

Biodistribution and clearance concerns, as inorganic components may accumulate in the liver or spleen.

High production costs and the need for specialized imaging facilities.

To overcome these barriers, ongoing research focuses on biodegradable theranostic agents, AI-guided imaging quantification, and standardized safety protocols for nanomedicine approval.

8.7 Future Prospects

Emerging developments include self-reporting nanoparticles that can emit fluorescent signals upon drug release and machine-learning–integrated systems capable of real-time interpretation of imaging data to

guide adaptive therapy. The convergence of nanotechnology, bioinformatics, and imaging sciences will be key to achieving next-generation personalized nanotheranostics for breast cancer.

9.Gene and immune-Nano therapy Approaches

9.1 Introduction

Gene therapy and immunotherapy have transformed cancer treatment, and their integration with nanotechnology offers improved targeting, stability, and intracellular delivery. In breast cancer, nanoparticle-assisted delivery of nucleic acids and immune agents helps overcome drug resistance, immune evasion, and tumor heterogeneity.

9.2 Nanoparticles for Gene Therapy

Nanocarriers protect fragile genetic materials like DNA, siRNA, and miRNA from degradation and enhance their cellular uptake.

- DNA and siRNA Delivery: Cationic liposomes and polymeric nanoparticles deliver siRNA targeting genes such as *Bcl-2* or *HER2*, inducing apoptosis in resistant cells. Gold-based and folate-modified systems further improve gene silencing and tumor targeting.
- CRISPR/Cas9 Delivery: Lipid nanoparticles carrying Cas9 mRNA and sgRNA enable precise genome editing, effectively suppressing oncogenic mutations like *PIK3CA* in HER2-positive breast cancer.
- MicroRNA Modulation: Nanocarriers delivering miRNA mimics (e.g., miR-34a) can inhibit metastasis and epithelial–mesenchymal transition in triple-negative breast cancer (TNBC).

9.3 Immuno-Nanotherapies

Nanoparticles enhance immunotherapy by improving the delivery of immune-stimulating agents and reducing off-target toxicity.

- Nanovaccines: Formulations containing tumor antigens (e.g., HER2 peptides) and adjuvants (e.g., CpG) boost dendritic cell activation and T-cell responses. Lipid-based mRNA nanovaccines are also promising for personalized cancer immunization.
- Immune Checkpoint Inhibitors: Nanoparticles co-delivering anti-PD-L1 antibodies or siRNA with chemotherapeutics enhance immune activation and tumor regression. Hybrid gold-lipid nanocarriers further combine gene silencing with photothermal therapy.
- Cytokine and Adjuvant Delivery: Nanocarriers carrying cytokines like IL-2 or IFN-γ enable localized release, stimulating immune cells while minimizing systemic toxicity.
- Combination Therapy: Co-delivery systems combining chemotherapy and immune agents (e.g., doxorubicin with CpG-DNA) induce both tumor shrinkage and immune memory, reducing recurrence.

9.4 Tumor Microenvironment (TME) Modulation

The suppressive tumor microenvironment—marked by hypoxia, acidity, and immune cell inhibition—reduces immunotherapy efficacy. Smart nanoparticles that release oxygen or reprogram macrophages can normalize the TME and enhance responses to checkpoint therapies. For instance, MnO_2 nanoparticles generate oxygen to improve T-cell infiltration and boost PD-1 blockade efficacy.

9.5 Clinical Progress and Challenges

Several nanocarrier-based gene and immunotherapies are in early clinical evaluation, such as lipid nanoparticles delivering siRNA (e.g., VEGF-targeting systems) and mRNA cancer vaccines adapted from COVID-19 platforms. Despite encouraging results, challenges include large-scale production, reproducibility, and long-term safety assessment.

9.6 Future Perspectives

Next-generation nanoplatforms aim to integrate gene editing, drug delivery, and immunomodulation into single "all-in-one" systems. Personalized nanovaccines tailored to patient-specific tumor antigens, along with AI-driven nanoparticle design, promise enhanced precision, safety, and treatment outcomes. Collaboration between researchers, clinicians, and regulatory bodies will be vital to accelerate clinical translation.

10.Challenges and Limitations

Despite significant progress, the clinical translation of targeted nanoparticle systems for breast cancer therapy faces major challenges. Tumor heterogeneity, dense extracellular matrices, and irregular vasculature limit nanoparticle penetration and retention, reducing treatment effectiveness. Technical barriers such as inconsistent large-scale synthesis, stability issues, and potential off-target toxicity further hinder progress. High production costs, complex regulations, and limited data on long-term biocompatibility also delay clinical adoption. Addressing these issues requires collaborative research to refine nanoparticle design, enhance targeting accuracy, and establish standardized manufacturing and regulatory guidelines for safe, effective translation into clinical practice.

11.Future perspectives:

The future of targeted nanoparticles in breast cancer therapy focuses on developing multifunctional and intelligent nanocarriers that combine diagnosis and treatment, known as theranostics. Stimuli-responsive systems reacting to tumor-specific cues like pH, temperature, or enzymes promise higher precision and reduced side effects. Incorporating AI and machine learning can further optimize nanoparticle design and predict behavior in the body. Biomimetic and personalized approaches, such as exosome- or immune cell–based nanocarriers, offer improved compatibility and selectivity. Achieving clinical success will require scalable production, strict quality control, and unified regulatory standards, supported by strong collaboration between researchers, clinicians, and policymakers.

12.Conclusion

Targeted nanoparticle-based therapies represent a major advancement in breast cancer treatment by enabling precise drug delivery, minimizing systemic toxicity, and improving therapeutic outcomes. These systems utilize tumor-specific receptors and microenvironmental traits to enhance selectivity and efficacy. However, large-scale production, long-term safety, and biological complexity continue to hinder clinical translation. Progress in nanoparticle design, functionalization, and safety evaluation—combined with personalized medicine, AI, and advanced imaging—will be crucial for developing multifunctional nanoplatforms. Interdisciplinary collaboration and standardized assessment methods will ultimately drive their successful integration into clinical practice.

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