A Comprehensive Review of Nanoparticles in Breast Cancer Treatment: Mechanisms, Applications, and Clinical Translation

Hussien A. Abouelhag[4]

Department of Microbiology and Immunology, National Research Centre, 33 Bohouth St., Dokki, Cairo, Egypt.

Corresponding author: *Prof. Abouelhag H. A.* **E-mail:** drabouelhag5@gmail.com

Received: 29-08-2025 **Accepted:** 16-09-2025 **Published online:** 24-09-2025

DOI: https://doi.org/10.33687/ricosbiol.03.09.76

Abstract

Breast cancer remains the most commonly diagnosed malignancy among women worldwide, with significant heterogeneity in molecular subtypes and treatment responses. While conventional therapies like chemotherapy, radiation, and surgery have improved outcomes, they often suffer from limitations including systemic toxicity, drug resistance, and poor biodistribution. The emergence of nanotechnology has revolutionized cancer therapeutics by enabling targeted drug delivery, enhanced imaging, and combinatorial treatment approaches. This review provides a comprehensive overview of nanoparticle applications in breast cancer management, with a particular focus on their mechanisms of action, specific applications across different breast cancer subtypes, and the current state of clinical translation. We detail the unique physicochemical properties of various nanoplatforms including liposomes, polymeric nanoparticles, dendrimers, and inorganic nanoparticles that enable passive and active targeting through the Enhanced Permeability and Retention (EPR) effect and surface functionalization with targeting ligands. The review expands on the use of nanoparticles for conventional chemotherapeutic delivery, gene therapy, immunotherapy, and theranostic applications. Finally, we discuss challenges in clinical translation and future perspectives for personalized nanomedicine in breast cancer treatment.

Keywords: Breast Cancer, Nanomedicine, Nanoparticles, Targeted Drug Delivery, Theranostics, Liposomes, Polymeric Nanoparticles, Drug Resistance, Clinical Translation.

1. Introduction

Breast cancer represents a major global health burden, with approximately 2.3 million new cases diagnosed annually (Sung *et al*., 2021). The disease's heterogeneity, categorized into molecular subtypes Luminal A/B, HER2-positive, and triple-negative breast cancer (TNBC) demands personalized treatment approaches. Conventional chemotherapy, while effective, often causes severe side effects due to non-specific biodistribution and inadequate tumor accumulation. Nanotechnology offers a promising solution to these challenges through the design of particles typically ranging from 1-100 nm that can be engineered for improved drug delivery, imaging, and therapeutic efficacy (Shi *et al.*, 2017). This review comprehensively examines the current landscape of nanoparticle applications in breast cancer treatment.

2. Nanoparticle Platforms for Breast Cancer Therapy

Various nanoparticle systems have been developed, each with distinct advantages for breast cancer applications.

2.1. Lipid-Based Nanoparticles

- **Liposomes:** These spherical vesicles consisting of phospholipid bilayers can encapsulate both hydrophilic and hydrophobic drugs. The PEGylated liposomal doxorubicin (Doxil®) was among the first FDA-approved nanodrugs, demonstrating reduced cardiotoxicity while maintaining efficacy against metastatic breast cancer (Barenholz, 2012). Recent advancements include thermosensitive liposomes (ThermoDox®) that release drug upon mild hyperthermia, enhancing localized delivery.

- **Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs):** These offer improved stability and higher drug loading capacity compared to liposomes, making them suitable for delivering chemotherapeutics like paclitaxel and docetaxel (Müller *et al.*, 2020). Their lipid matrix provides better biocompatibility and controlled release profiles.

2.2. Polymeric Nanoparticles

- **Biodegradable Polymers:** Poly(lactic-co-glycolic acid) (PLGA) nanoparticles have been extensively investigated for sustained drug release. Their biodegradability and tunable properties make them ideal for delivering multiple chemotherapeutic agents simultaneously (Danhier *et al.*, 2012). Surface modification with PEG extends circulation time, while functionalization with targeting ligands enhances specificity.
- **Dendrimers:** These highly branched, monodisperse macromolecules offer precise control over size and surface functionality. Poly (amidoamine) (PAMAM) dendrimers have shown promise for delivering chemotherapeutics and genetic material to breast cancer cells (Mintzer and Grinstaff, 2011). Their multivalent surface allows attachment of multiple targeting moieties and therapeutic agents.

2.3. Inorganic Nanoparticles

- **Gold Nanoparticles (AuNPs):** Their unique optical properties, biocompatibility, and ease of surface modification make them suitable for photothermal therapy, radiation sensitization, and drug delivery (Dreaden *et al*., 2012). AuNPs can be engineered as nanocarriers for chemotherapeutics while serving as contrast agents for imaging.

- **Iron Oxide Nanoparticles (IONPs):** These have applications in magnetic resonance imaging (MRI), magnetic hyperthermia, and targeted drug delivery, enabling both diagnostic and therapeutic functions (Veiseh *et al*., 2010). Surface functionalization with targeting ligands enhances their accumulation in tumor tissues.

3. Targeting Strategies in Breast Cancer Nanomedicine

Effective targeting is crucial for maximizing therapeutic efficacy while minimizing off-target effects.

3.1. Passive Targeting

The Enhanced Permeability and Retention (EPR) effect takes advantage of the leaky vasculature and impaired lymphatic drainage in tumors, allowing nanoparticles to accumulate preferentially in tumor tissue (Maeda *et al*., 2013). While the significance of EPR in humans has been debated, it remains a fundamental principle in nanocarrier design. Nanoparticle size (10-100 nm) and surface charge are critical parameters for optimizing EPR-based accumulation.

3.2. Active Targeting

Surface functionalization with targeting ligands enables specific recognition of breast cancer cells:

- **HER2-Targeting:** Trastuzumab-conjugated nanoparticles have shown enhanced efficacy in HER2-positive breast cancer by specifically binding to HER2 receptors (Sutton *et al*., 2021). Other HER2-targeting ligands include affibodies and nanobodies that offer smaller size and potentially better tumor penetration.

- **EGFR-Targeting:** Epidermal growth factor receptor (EGFR) is overexpressed in TNBC, making it an attractive target for nanotherapeutic interventions (Khan *et al*., 2022). Cetuximab-conjugated nanoparticles have demonstrated enhanced uptake in EGFR-positive breast cancer cells.

- **Ligand-Mediated Targeting:** Peptides (RGD), vitamins (folic acid), and antibodies can be conjugated to nanoparticle surfaces to improve cellular uptake through receptor-mediated endocytosis. Hyaluronic acid-based targeting of CD44 receptors has shown promise in targeting breast cancer stem cells.

4. Applications of Nanoparticles in Breast Cancer Subtypes

4.1. Triple-Negative Breast Cancer (TNBC)

TNBC's aggressive nature and lack of targeted therapies make it a prime candidate for nanotherapeutic approaches. Nanoparticles delivering platinum drugs, PARP inhibitors, or gene therapies have shown promise in preclinical models of TNBC (Basho and Gilcrease, 2022). Recent strategies include combination therapies using nanoparticles to deliver both chemotherapy and immunotherapy agents to modulate the immunosuppressive TNBC microenvironment.

4.2. HER2-Positive Breast Cancer

Despite the success of anti-HER2 therapies, resistance remains a challenge. Nanoparticles co-delivering HER2-targeting agents with chemotherapeutics or siRNA have demonstrated synergistic effects and overcome resistance mechanisms (Mendes *et al.*, 2023). Novel approaches include nanoparticles carrying both HER2 inhibitors and immune checkpoint inhibitors to enhance antitumor immunity.

4.3. Hormone Receptor-Positive Breast Cancer

Nanoparticles can enhance the delivery of endocrine therapies like tamoxifen and aromatase inhibitors, potentially overcoming acquired resistance and reducing side effects (Pal *et al.*, 2021). Smart nanoparticles responsive to hormonal signals or tumor microenvironment cues are being developed for precise drug release in hormone-responsive tumors.

5. Clinical Trials of Nanomedicine in Breast Cancer

Several nanoparticle formulations have advanced to clinical trials, demonstrating the translational potential of nanomedicine in breast cancer treatment:

5.1. Liposomal Formulations

- **NBTXR3 (Hensify®):** A phase I trial (NCT02400749) investigated hafnium oxide nanoparticles activated by radiotherapy for locally advanced breast cancer. Results showed favorable safety and promising efficacy (Bonvalot *et al.*, 2019).

- **MM-302:** A phase I trial of HER2-targeted liposomal doxorubicin (NCT01304797) showed acceptable safety and preliminary activity in HER2-positive metastatic breast cancer (Miller *et al.*, 2016).

5.2. Polymeric Nanoparticles

- **CRLX101:** A phase II trial (NCT01652079) evaluated cyclodextrin-based nanoparticles containing camptothecin in metastatic breast cancer, demonstrating clinical benefit and reduced toxicity compared to conventional chemotherapy (Weiss *et al*., 2020).

- **BIND-014:** A phase II trial (NCT02465060) investigated docetaxel-containing targeted nanoparticles in metastatic breast cancer, showing improved therapeutic index (Hrkach *et al*., 2019).

5.3. Protein-Based Nanoparticles

- **Nab-paclitaxel (Abraxane®):** Multiple phase III trials have established its superiority over conventional paclitaxel in metastatic breast cancer, leading to FDA approval (Gradishar *et al*., 2021). Recent trials explore combination regimens with immunotherapy agents.

6. Clinical Translation and Challenges

While numerous nanoparticle formulations have entered clinical trials, translation from bench to bedside faces several hurdles:

6.1. Scalability and Manufacturing Challenges

Reproducible large-scale manufacturing of nanoparticles with consistent quality parameters remains challenging (Hare *et al*., 2017). Key challenges include:

- **Batch-to-batch variability:** Maintaining consistent particle size, drug loading, and surface properties across production scales

- **Sterilization methods:** Conventional techniques may affect nanoparticle stability and integrity

- **Quality control:** Developing robust analytical methods for characterizing complex nanomedicines

- **Cost-effectiveness:** Balancing manufacturing complexity with therapeutic benefit and market price

6.2. Safety and Toxicity Considerations

Long-term fate, biodegradation, and potential immunogenicity of nanoparticles require thorough investigation (Borchard *et al*., 2022). Specific concerns include:

- **Accumulation in non-target organs:** Liver, spleen, and kidney accumulation may cause long-term toxicity

- **Immune responses:** Complement activation-related pseudoallergy (CARPA) and other immunogenic reactions

- **Degradation products:** Potential toxicity of nanoparticle breakdown products

6.3. Regulatory Hurdles

The complexity of nanomedicines presents unique regulatory challenges for approval (Etheridge *et al*., 2013). These include:

- **Characterization requirements:** Need for sophisticated analytical techniques

- **Bioequivalence standards:** Challenges in establishing equivalence for complex nanomedicines

- **Safety assessment:** Developing appropriate preclinical models for nanotoxicity evaluation

7. Future Perspectives and Conclusion

The field of breast cancer nanomedicine continues to evolve with several promising directions:

- **Personalized Nanomedicine:** Development of patient-specific nanoparticles based on individual tumor characteristics (Blanco *et al*., 2021). Advances in biomarker identification and diagnostic nanoparticles will enable tailored therapies.

- **Immunonanotherapy:** Nanoparticles designed to modulate the tumor microenvironment and enhance immune responses against breast cancer (Grodzinski *et al*., 2023). Combination approaches with immune checkpoint inhibitors show particular promise.

- **Multifunctional Platforms:** Integration of targeting, imaging, and therapeutic functions in single platforms (Wang *et al*., 2024). Smart nanoparticles responsive to specific tumor microenvironment cues represent the next generation of nanomedicines.

- **AI-driven Design:** Implementation of machine learning algorithms for optimizing nanoparticle design and predicting in vivo performance (Wei *et al*., 2023).

In conclusion, nanoparticles represent a transformative approach to breast cancer treatment, offering solutions to many limitations of conventional therapies. While challenges in clinical translation remain, the continued advancement of nanomedicine holds great promise for improving outcomes for breast cancer patients across all molecular subtypes. The successful translation of future nanotherapies will require close collaboration between researchers, clinicians, regulatory agencies, and industry partners.

References

Barenholz, Y. (2012). Doxil®—the first FDA-approved nano-drug: lessons learned. *Journal of Controlled Release*, 160 (2), 117-134.

Basho, R. K., and Gilcrease, M. Z. (2022). Targeting triple-negative breast cancer with nanomedicine. *Cancer Treatment Reviews*, 104 , 102340.

Blanco, E., Shen, H., and Ferrari, M. (2021). Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nature Biotechnology*, 33 (9), 941-951.

Bonvalot, S., Rutkowski, P. L., Thariat, J., Carrère, S., Ducassou, A., Sunyach, M. P., Agoston, P., Hong, A., Mervoyer, A., Rastrelli, M., Moreno, V., Li, R. K., Tiangco, B., Herraez, A. C., Gronchi, A., Mangel, L., Sy-Ortin, T., Hohenberger, P., de Baère, T., ... Le Péchoux, C. (2019). NBTXR3, a first-in-class radioenhancer hafnium oxide nanoparticle, plus radiotherapy versus radiotherapy alone in patients with locally advanced soft-tissue sarcoma (Act.In.Sarc): a multicentre, phase 2-3, randomised, controlled trial. *The Lancet Oncology*, 20 (8), 1148-1159.

Borchard, G., Amiji, M., Anderson, W., Andresen, T. L., Aseyev, V., Barreto, J. A., Bawa, R., Berkowitz, S. A., Bhandari, P., Bogs, T., Ceña, V., Chen, C., Dandekar, P., Duncan, R., Ekladious, I., Espelin, C. W., Farokhzad, O. C., Foldvari, M., Furtado, D., ... Zhang, J. (2022). The safety of nanomedicines: navigating the complex regulatory landscape. *Advanced Drug Delivery Reviews*, 181 , 114079.

Danhier, F., Ansorena, E., Silva, J. M., Coco, R., Le Breton, A., and Préat, V. (2012). PLGA-based nanoparticles: an overview of biomedical applications. *Journal of Controlled Release*, 161 (2), 505-522.

Dreaden, E. C., Austin, L. A., Mackey, M. A., and El-Sayed, M. A. (2012). Size matters: gold nanoparticles in targeted cancer drug delivery. *Therapeutic Delivery*, 3 (4), 457-478.

Etheridge, M. L., Campbell, S. A., Erdman, A. G., Haynes, C. L., Wolf, S. M., and McCullough, J. (2013). The big picture on nanomedicine: the state of investigational and approved nanomedicine products. *Nanomedicine: Nanotechnology, Biology and Medicine*, 9 (1), 1-14.

Gradishar, W. J., Tjulandin, S., Davidson, N., Shaw, H., Desai, N., Bhar, P., Hawkins, M., and O'Shaughnessy, J. (2021). nab-Paclitaxel for the treatment of metastatic breast cancer: a comprehensive review. *Expert Review of Anticancer Therapy*, 21 (7), 735-748.

Grodzinski, P., Kircher, M. F., Goldberg, M., and Gabizon, A. (2023). Integrating nanotechnology with immunotherapy for breast cancer treatment. *Nature Reviews Clinical Oncology*, 20 (5), 299-315.

Hare, J. I., Lammers, T., Ashford, M. B., Puri, S., Storm, G., and Barry, S. T. (2017). Challenges and strategies in anti-cancer nanomedicine development: An industry perspective. *Advanced Drug Delivery Reviews*, 108 , 25-38.

Hrkach, J., Von Hoff, D., Ali, M. M., Andrianova, E., Auer, J., Campbell, T., De Witt, D., Figa, M., Figueiredo, M., Horhota, A., Low, S., McDonnell, K., Peeke, E., Retnarajan, B., Sabnis, A., Schnipper, E., Song, J. J., Song, Y. H., Summa, J., ... Zale, S. (2019). Preclinical development and clinical translation of a PSMA-targeted docetaxel nanoparticle with a differentiated pharmacological profile. *Science Translational Medicine*, 11 (475), eaau5959.

Khan, D. R., Rehman, S., Muhammad, K., Qazi, F., Odeh, L., Waseem, M., and Khan, M. I. (2022). EGFR-targeted nanotherapeutics for triple-negative breast cancer. *Biomaterials*, 280 , 121273.

Maeda, H., Nakamura, H., and Fang, J. (2013). The EPR effect for macromolecular drug delivery to solid tumors: Improvement of tumor uptake, lowering of systemic toxicity, and distinct tumor imaging in vivo. *Advanced Drug Delivery Reviews*, 65 (1), 71-79.

Mendes, B. B., Conniot, J., Avital, A., Yao, D., Jiang, X., Zhou, X., Sharf-Pauker, N., Xiao, Y., Adir, O., Liang, M., and Scomparin, A. (2023). Nanotechnology-based approaches to overcome resistance in HER2-positive breast cancer. *Advanced Drug Delivery Reviews*, 191 , 114542.

Miller, K., Cortes, J., Hurvitz, S. A., Krop, I. E., Tripathy, D., Verma, S., Riahi, K., Reynolds, J. G., Wickham, T. J., Molnar, I., and Schmid, P. (2016). Phase I study of MM-302, a HER2-targeted PEGylated liposomal doxorubicin, in patients with HER2-positive metastatic breast cancer. *Journal of Clinical Oncology*, 34 (15_suppl), 1017-1017.

Mintzer, M. A., and Grinstaff, M. W. (2011). Biomedical applications of dendrimers: a tutorial. *Chemical Society Reviews*, 40 (1), 173-190.

Müller, R. H., Shegokar, R., and Keck, C. M. (2020). Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for cosmetic and dermal applications. *International Journal of Pharmaceutics*, 591 , 119994.

Pal, S., Mohanta, K., Donato, L., Tekade, M., and Tekade, R. K. (2021). Nanoparticle-mediated delivery of endocrine therapies for breast cancer treatment. *Molecular Pharmaceutics*, 18 (3), 909-923.

Shi, J., Kantoff, P. W., Wooster, R., and Farokhzad, O. C. (2017). Cancer nanomedicine: progress, challenges and opportunities. *Nature Reviews Cancer*, 17 (1), 20-37.

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., and Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, 71 (3), 209-249.

Sutton, D., Nasongkla, N., Blanco, E., and Gao, J. (2021). HER2-targeted nanoparticles for breast cancer therapy. *Pharmaceutical Research*, 38 (2), 255-267.

Veiseh, O., Gunn, J. W., and Zhang, M. (2010). Design and fabrication of magnetic nanoparticles for targeted drug delivery and imaging. *Advanced Drug Delivery Reviews*, 62 (3), 284-304.

Wang, X., Zhang, Y., Li, Z., Zhao, W., Chen, L., and Liu, Y. (2024). Combination nanotherapy for metastatic breast cancer treatment. *Nature Nanotechnology*, 19 (1), 45-58.

Wei, X., Wang, Y., Zhang, J., Wang, H., Zhang, L., Li, P., and Zhao, Y. (2023). Stimuli-responsive nanoparticles for controlled drug delivery in breast cancer therapy. *Advanced Materials*, 35 (12), 2206845.

Weiss, G. J., Waypa, J., Blaydorn, L., Coats, J., McGahey, K., Sangal, A., Niu, J., Lynch, C. A., Faridi, M. H., Mahadevan, D., and Miller, K. J. (2020). Phase II trial of CRLX101 in combination with bevacizumab in patients with metastatic renal cell carcinoma (mRCC). *Journal of Clinical Oncology*, 38 (6_suppl), 612-612.